Tuberculosis burden in Bangladesh: epidemiological estimates and people's perspectives

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**Tuberculosis burden in Bangladesh:**
epidemiological estimates and people’s perspectives

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Friday 12th September 2014
at 10.00 hours

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Tuberculosis burden in Bangladesh: 
epidemiological estimates and people’s perspectives

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CHAPTER 1

GENERAL INTRODUCTION
Mycobacterium tuberculosis (MTB), the micro-organism causing tuberculosis (TB) in humans, was first discovered by Robert Koch on March 24, 1882. After more than a hundred years, the World Health Organisation (WHO) declared a global emergency for tuberculosis in 1993 as the disease continued to be the major cause of death and sufferings to millions of people throughout the globe, particularly from the developing world. Since then, major efforts have been undertaken to control the disease by implementing a standardized TB-control strategy. This “Directly Observed treatment; Short Course (DOTS)” strategy contained five pillars with an emphasis on case-finding and treatment. The strategy was incorporated in the subsequent “STOP TB strategy” formulated in 2006, which adopted wider goals including the need for operational research and community empowerment in the fight against TB.

TB situation in Bangladesh

TB continues to be a major public health problem in Bangladesh. The country ranks 6th among the 22 high burden countries of the world according to the yearly WHO-estimates. The actual extent of the tuberculosis problem in Bangladesh is not known precisely, due to the lack of adequate epidemiological data on prevalence, incidence and mortality. The WHO estimate of prevalence was estimated with a very large uncertainty at 434 (218-721)/100,000 population for all types of TB. The estimated incidence remained stable for the last decade at 225 (185-268)/100,000 per year, while the mortality showed a very slow decline (Figure 1).

![Fig. 1: TB situation in Bangladesh 2013](image-url)
Despite an assumed country wide DOTS coverage and good treatment success rate, the TB-case notification rate stagnated, at around 150,000 new smear positive cases (SS+ve) each year from 2006 onwards (Figure 1).

Two-third of the TB patients detected in 2012 had new smear-positive pulmonary TB (PTB), while 15% had smear-negative PTB and 19% had extra pulmonary TB (EPTB). Three percent of the TB-cases were diagnosed in children. The proportion of retreatment cases was 4.6% among all cases notified in 2012. The prevalence of multi drug resistance (MDR) cases among new cases was 1.4 % (0.7-2.5%), and among retreatment cases 29% (24-34%).

Prevalence estimates obtained from surveys in Bangladesh varied widely. The available epidemiological data from the surveys in 1964-66 and in 1987-88 were re-analysed in 1997 in an attempt to reconcile the estimates of TB-prevalence. This resulted in an estimated prevalence of smear positive TB of 220/100,000 population in 1964-66 survey and 527/100,000 population in 1987-88 survey.

Similarly, the prevalence of infection estimates remained unclear in Bangladesh. The only tuberculin survey was conducted along with the 1964-66 prevalence survey, and provided an estimation of annual risk of tuberculous infection (ARTI) of 2.3%. It is this estimate which formed the basis of the yearly WHO estimates of the burden of TB in Bangladesh.

The social face of TB in Bangladesh is still complex and puzzling. For example, the difference in TB notifications between men and women appears to be relatively large in the country, with an Female/Male ratio in notified cases of .50 in smear positive cases in 2012. Other local studies reported this ratio as low as 0.39. It is debated if this difference is a result of differences in exposure, accessibility to services, cough production, or smoking habits. Also the role of stigma might have a differential effect on men and women. Studies in Bangladesh suggest that stigma is more prominent in women than men, precluding adequate identification in the former.

One of the reasons for providing DOTS free of cost is that everyone with the disease can access treatment when needed, particularly the poorer sections of the population. Case notification data segregated by socio economic strata is not available in Bangladesh but inequities in accessing services in other sectors of the health services suggest that inequity in service utilization might also be a challenging issue for the TB control programme. It has been recognized that TB control needs to focus beyond therapeutic strategies to include poverty and
tackling the social determinants of TB.\textsuperscript{17} There is a need to obtain better information on socio-economical factor influencing access to TB-services in Bangladesh.

The current DOTS program in Bangladesh depends on passive case finding for TB treatment. The estimated case notification proportion of new smear positive PTB of around 70\% since 2006 suggests that a substantial portion of cases still remains outside DOTS and is probably being treated in the private sector or not accessing care at all.\textsuperscript{19} Passive case finding is influenced by patient’s awareness, accessibility and availability of health services. Knowledge on TB disease, its diagnosis and treatment therefore is an important factor for the management and outcomes. Even when TB-services are accessed, the response of the health staff determines further actions. To improve case notification, there is a need to address the knowledge gaps related to care seeking, and inappropriate actions of care providers in their interactions with potential TB-cases.

\textbf{Bangladesh: Population, health systems and TB control services}

Bangladesh has a total 155 million people living in 147,570 Sq. Km areas, giving rise to a density of 1142 persons per /Km\textsuperscript{2}. About one third of the population lives below the poverty line. The life expectancy at birth is 70 years for both sexes, for male this is 68 and for females 72 years. Bangladesh is one of the low income countries of the world with a GDP-per capita of 2100 USD in 2012. The country has many social and economical problems, political instability, poor infrastructure, corruption, inadequate power supplies, and slow implementation of economic reforms.\textsuperscript{20}

The country is divided into 7 divisions, 64 districts, 460 Upazila (sub-districts with a range of population size 300,000 to 400,000), of which 397 are rural and 63 are semi-urban. In addition, there are 4 main cities run by city corporations, and other smaller municipalities comprising the urban or metropolitan population of the country. The health system in Bangladesh is pluralistic in nature, where many stakeholders, public and private, modern and traditional, coexist and work.\textsuperscript{21} In Bangladesh, there are two types of health care providers: formal and informal. The informal sector includes a large number of unlicensed and unqualified or semi-qualified private practitioners like Village Doctors practicing allopathic medicine, homoeopathic doctors, and traditional healers. Among these, village doctors with very little or no formal training are the dominant type.\textsuperscript{22,23} It is estimated that nearly 95\% of the entire health workforce in Bangladesh is made up by the informal sector, the number of which is steadily increasing.\textsuperscript{24,25} Many NGOs are working in Bangladesh, including...
some of the largest in the world (BRAC, Grameen, ASA and Proshika). The private for-profit sector is large and growing at an exponential rate of about 15% per year. The number of private practitioners is estimated to be 3.6 per 1000 population, approximately 5 physicians and 2 nurses per 10,000 people, while there are 12 village doctors and 11 drug sellers per 10,000.\textsuperscript{25}

The basic primary health care unit in Bangladesh is the Upazila Health Complex at Upazila level. It provides out-patient, inpatient and emergency services. Secondary and tertiary health care is provided by general and specialised hospitals at district and divisional levels. In the private health sector, in addition to the private licensed providers (medical graduate or post graduate specialists) clinics and hospitals are becoming more visible with the advent of time. The private traditional and homeopathic providers are available in most of the villages.

**TB control in Bangladesh**

In the pre-DOTS era, TB control in Bangladesh was vertical and based in a limited number of large hospitals in different districts of the country. Chest x-ray and long-term therapy was the mainstay of diagnosis and treatment. In 1993, the government of Bangladesh adopted the DOTS strategy for TB control and started to implement its components throughout the country. This occurred initially in rural areas and was only from 2003 onwards scaled-up to the urban areas. One important feature in expanding TB services was including NGOs in TB-control activities from the beginning. The government commitment continued with subsequent annual development plans. TB-control activities were further strengthened with the availability of funding support from Global Fund for TB, AIDS and Malaria (GFATM) since 2003.\textsuperscript{26}

**The National TB Control Programme**

The services of the National Tuberculosis Control Programme (NTP) are organized under a sub directorate called Mycobacterium Disease Control (MBDC) which reports directly under the governance of the Directorate General of Health Services (DGHS). At the district level, the Civil Surgeon (CS) heads the health administration, and at the Upazila or sub-district level, the Upazila Health and Family Planning Officer (UHFPO) is responsible for TB services. This latter is the basic unit for diagnosis and management of TB patients. Every Upazila has a central centre where microscopy for TB diagnosis is performed and other DOTS-activities
are implemented. This centre is run by government or NGO staff. Additional DOTS services are provided at lower level facilities by Health Assistants, and occasionally by trained village doctors.\textsuperscript{27,28}

The TB services are organised slightly different in urban areas. They are provided under the Urban Primary Health Care Project (UPHCP) which falls under the Ministry of Local government, rural development and cooperative (MoLGRDC). In addition to the 460 Upazila Health Complexes of the country, free TB series are also available through 44 chest diseases clinics at district levels, 11 chest disease hospitals, all 64 districts and all medical college hospitals, 264 urban health centres, prisons and in many garments factory work places.\textsuperscript{5}

\textbf{General objective and outline of this thesis}

The overall objective of this thesis is to describe the epidemiology of tuberculosis in Bangladesh and related programmatic issues, and to assess and understand TB in its socio-economic perspectives.

Specific objectives are:

1. To assess the burden of tuberculosis in Bangladesh;
   i. Describe the prevalence of smear positive pulmonary TB in adults (\geq 15 years)
   ii. Estimate the prevalence of TB-infection among children (<15 years)

2. To examine the access of the National Tuberculosis Control Programme (NTP) by different segments of community population.

3. To assess the care seeking behaviour of the individuals with chronic cough (Suspected TB case) and response of the health system to this care seeking

4. To assess the knowledge on TB and health services relating to TB (Programmatic aspects) in TB cases and general population

While focusing on the epidemiological and technical aspects of the disease this thesis also tries to understand TB disease and infection in its social perspectives: in terms of its control and prevention activities adopted and implemented by the NTP, people’s awareness of the disease, and their care seeking pattern and how all these impact on the outcomes of the control programme.
In chapter 2 we describe the burden of the disease in the country as obtained through the national tuberculosis prevalence survey 2007-2009. We report an estimate of prevalence by different sub groups of population; discuss the results in the light of methodological constraints and implications for the NTP, Bangladesh.

In chapter 3 we describe the results of the tuberculin skin testing (TST) survey, which was carried out along with the disease prevalence survey throughout the country. We report the estimate of the prevalence of infection and the associated Annual Risk of Tuberculous Infection (ARTI) in two age groups of children (5-10 years and 10-14 years). These estimates are discussed in relation to the socio economic position of the persons under survey.

In chapter 4 we discuss the societal and programmatic aspects of tuberculosis in Bangladesh. We describe the access and use of free NTP services by different section of the population using the SEP in the general population, the population under the survey, the detected cases and a sample of cases detected routinely under NTP.

In chapter 5 we elaborate on the care seeking of patients detected actively in the national survey or passively by the NTP. We illustrate the care seeking from the first point of care to the subsequent fourth point of care. The role and practice of the care providers is compared among the formal (Licensed or acceptable to the programme) and informal (unlicensed and unacceptable to the programme) providers wherever the care was sought by the TB cases.

In chapter 6 we discuss the knowledge on TB and on some important programmatic aspects among TB and Non TB cases selected from the same localities during the national survey.

In chapter 7 we describe an operational aspect of TB programme focusing on the quality of the sputum specimen collected during the survey for microscopic detection of TB. We compare its macroscopic features with microscopic tests to validate the quality of sputum.

Chapter 8 provides a general discussion on the findings in this thesis in relation to the TB situation of Bangladesh, methodological issues, and implications of the findings for the TB control and further research.
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CHAPTER 2

PREVALENCE OF SMEAR-POSITIVE TUBERCULOSIS IN PERSONS AGED ≥ 15 YEARS IN BANGLADESH: RESULTS FROM A NATIONAL SURVEY, 2007-2009

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Summary

The aim of this study was to determine the nationwide prevalence of smear-positive tuberculosis (TB) in Bangladesh. A multi-stage cluster survey of a random sample of persons aged ≥15 years was included in 40 clusters (20 urban, 20 rural). Two sputum samples were collected from study participants and tested initially by fluorescence microscopy and confirmed by the Ziehl-Neelsen method. The crude and adjusted prevalence rates and 95% confidence intervals (CIs) were calculated using standard methods. A total of 33 new smear-positive TB cases were detected among 52,098 individuals who participated in the study. The average participation rate was over 80%. The overall crude prevalence of new smear-positive TB in persons aged ≥15 years was estimated as 63.3/100,000 (95% CI 43.6-88.9) and the adjusted prevalence was 79.4/100,000 (95% CI 47.1-133.8). TB prevalence was higher in males (n=24) and in rural areas (n=20). The prevalence was highest in the 55-64 years age group (201/100,000) and lowest in 15-24 years age group (43.0/100,000). The prevalence was higher in persons with no education (138.6/100,000, 95% CI 78.4-245.0). The overall prevalence of smear-positive TB was significantly lower than the prevalence estimate of the previous nationwide survey in Bangladesh in 1987-1988 (870/100,000).

Key Words: Bangladesh; epidemiology; tuberculosis (TB)
Introduction

Tuberculosis (TB) is a major cause of morbidity and mortality globally with an estimated 9.4 million incident cases, 14 million prevalent cases, 1.3 million deaths from TB in HIV-negative and 0.38 million deaths in HIV-positive persons in 2009.\(^1\) Currently, Bangladesh ranks sixth in the 22 high-burden countries, with an estimated annual incidence of all forms of TB of 360,000 cases (225/100,000) and 83,000 deaths (51/100,000) annually.\(^1\) There is limited systematically collected recent epidemiological data from Bangladesh. Two previous national TB prevalence surveys were conducted in 1964-1966 and in 1987-1988. The 1964-1966 survey estimated a prevalence of sputum smear-positive pulmonary TB of 318/100,000 population in symptomatic individuals aged ≥15 years, while the 1987-1988 survey reported a much higher prevalence of 870/100,000 population in the same age group.\(^2,3\) Directly observed treatment, short course (DOTS) had been implemented in Bangladesh in 1993 and these surveys were conducted before implementation of DOTS. Several other smaller local surveys were conducted both in and outside the DOTS programme areas which reported estimates of prevalence of smear-positive TB ranging from 24 to 95/100,000 population.\(^4-6\) The results of these surveys should be interpreted cautiously since they all used different methods and populations.

Bangladesh has achieved commendable success in TB control activities with nationwide coverage of DOTS: >70% case detection rate and >90% treatment success rate.\(^7\) The case detection rate is based on the estimated incidence of TB which cannot be assessed directly. Instead, the incidence is approximated by extrapolating data from the 1964-1966 and 1987-1988 prevalence surveys and infection rates.\(^2,3\) This leads to considerable uncertainties, which together with the rapid increase in DOTS coverage, population growth and involvement of nongovernmental organizations (NGOs) and private sectors in TB control activities necessitates a reassessment of the TB situation in Bangladesh. The current study was undertaken with the objective of determining the prevalence of new smear-positive TB in Bangladesh and its distribution in different subgroups of the population.

Materials and methods

At the request of the National Tuberculosis Control Programme (NTP), Bangladesh, the World Health Organization (WHO) commissioned the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) to implement the national tuberculosis prevalence survey. The survey was conducted during October 2007-
March 2009. This was a cross-sectional community-based cluster survey and included all individuals aged ≥15 years who slept the previous night in a selected household within 40 selected clusters.

**Sample size calculation and outcome variable(s)**

The sample estimation was based on the total population of Bangladesh excluding the Chittagong Hill Tracts (1.2% the total population) which could not be included due to security issues. In 2001, the population of Bangladesh was 123,851,120, divided over six divisions which are in turn divided into 64 districts. The smallest administrative unit is the *mauza* in rural areas and the *mahallah* in urban areas. In total, there were 59,990 *mauzas/mahallas*.\(^1\)

According to the results of previous prevalence surveys and case notification rates, we assumed the prevalence of smear-positive TB to lie between 100 and 200/100,000 population. The sample size calculation for the survey was based on an estimated prevalence of 145/100,000 population, a desired precision of 25%, and a participation rate of 90%, leading to a required sample size of 47,000. With a cluster size of 1250 and a between-cluster coefficient of 0.25, the design effect was estimated to be 1.11, leading to an overall sample size of 50,300.\(^9\) To accommodate the 10% non-participation, we targeted 1400 adult individuals in each of the 40 clusters. Figure 1 shows the distribution of study sites.

**Sampling method**

A separate sampling frame was constructed for urban and rural strata. Sampling was performed proportionally to the population size with an *upazila* (subdistrict) as the primary sampling unit (PSU). Twenty PSUs were selected from each stratum. In each PSU one *mauza/mahallah* was randomly selected as a study cluster. The starting point for inclusion of households was randomly chosen after which households were added in a consecutive manner. Addition of households was stopped when the required sample size of eligible adults (1400 per cluster) was reached. All adult members (≥15 years) of these households were eligible for inclusion if they slept in that household the night before the visit of the census team.

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\(^{1}\) *Mauza* (in rural areas) corresponds approximately to a village; *mahalla* (in urban area); corresponds to an urban neighbourhood. *Mauzas* and *mahallas* are strictly delineated geographical areas.
Census taking

Two field teams collected data from two different clusters at the same time. They visited each household within the cluster to enumerate the study population, and to obtain information on sex, age, education level, presence of cough, and previous TB treatment of all individuals aged ≥15 years of the household.
Sputum sample collection

In each field site the field team visited all listed households. They first explained the study and the procedures, and thereafter obtained written informed consent from all adult individuals. All eligible participants were asked to provide a spot (at that moment) and a morning sputum specimen, which were examined by fluorescence microscopy (FM) at the field site. Samples positive by FM, were reexamined by Ziehl-Neelsen (ZN) microscopy. When only one of these specimens showed acid-fast bacilli, a third specimen was collected for examination. If this was negative for acid-fast bacilli, a chest X-ray was performed. All sputum specimens were labeled with a unique identifier of the respondent, and stored under cool conditions until their arrival at the field site laboratory. The team made a return visit to the households on the following morning to collect sputum samples if a participant had been absent.

Case definition

The case definition of a smear-positive TB patient was any person with either two positive samples by ZN microscopy or one positive sample by ZN microscopy and a chest X-ray suggestive for TB (Figure 2). This definition is similar to the one used in the TB control programme. It was assumed that individuals who were unable to produce a sputum sample did not have smear-positive TB. Additional information on sociodemographic, economic and care-seeking practices were also collected. The participants were asked if they had any cough on the day of the visit. If they answered yes, the interviewer enquired about the duration of the cough.

Laboratory procedure

Immediately after arrival at the field laboratory, the sputum specimens were assessed for macroscopic characteristics (colour, amount, nature). This information was included in the laboratory register. The samples were processed for FM, stained with auramine (0.1%, stained for 15 min) and examined by FM microscope. Slides positive were re-stained on the same day and re-examined with ZN for confirmation. All results were registered in the laboratory register. Specimens with evidence of acid-fast bacilli were stored in a cool place until transport to icddr,b for culture and drug susceptibility testing. Culture was performed using Löwenstein-Jensen solid media. Drug susceptibility testing was performed using the proportion method. The concentrations of anti-TB drugs tested were as follows: 0.2 mg/l isoniazid, 40 mg/l rifampicin, 2 mg/l ethambutol and 4 mg/l streptomycin. The specimens were kept at 4 °C after collection and were transported to the laboratory in a cool box within 24 h. No transport medium was used.
Quality assurance

The completeness and quality of the collected data was ensured by regular and routine supervision, checking and monitoring. All field and field laboratory data forms were routinely rechecked by one immediate supervisor and further checked by the team leader. Data transfer was performed in the evening in presence of all team members. Each team leader prepared an update of status which was displayed each day on a noticeboard showing the progress of the field work. A strong supervision structure was established for the survey consisting of field and central level supervisors. The study investigators and the senior field research officer
monitored the activities on a day-to-day basis and undertook routine field visits and repeated census taking on sample basis. Any discordance was discussed and rectified. The national steering committee provided necessary inputs on design, implementation, logistic support and supervision of the study activities on an ongoing basis.

Finally, an independent international expert made supervisory visits under the auspices of WHO technical support twice during the survey; once at the beginning and once when the survey moved into the Dhaka City field data collection period. One month after completion of the survey another monitoring visit was made to five randomly selected clusters and interviews were conducted in the selected areas about the survey in order to check the validity of the information and survey procedure.

All slides positive with ZN microscopy at the field laboratory were sent to icddr,b where they were re-stained with ZN and examined. Discordant results were checked by another microscopist blinded to the initial result. All positives and 2.5% of the negative slides by FM were sent to the Damien Foundation (the leading TB research organization in Bangladesh) for re-examination with FM. All identified cases were referred to a nearby DOTS centre for initiation of treatment and follow-up.

**Statistical approach**

Data analysis was performed using the statistical package Stata v. 10.0 (StataCorp., USA). The crude prevalence was estimated as number of cases detected among the participating population and expressed as per 100,000 population. The corresponding 95% confidence interval (CI) was calculated by Poisson regression. Adjusted analyses were based on a weighted estimation of the prevalence. The participation weight assigned to an adult respondent was the product of a stratification weight and an attrition weight. The stratification weight was the inverse of the probability of being included from the rural or urban sampling frame. The participation weight was the inverse of the probability of actually participating in the study when being eligible, which was assessed by logit estimation based on the variables age and sex. With these weights the study population was comparable to the target population of all individuals aged ≥15 years. The overall weight (the product of the stratification weight and the participation weight) was scaled to the size of the target population to ensure that statistical tests were conducted on the
appropriate number of degrees of freedom. Further analyses were performed using the complex cluster survey analysis option in Stata.

**Results**

The field data collection was conducted from October 2007 to March 2009. Figure 3 summarizes the number of people surveyed, number of people eligible to participate, number of people that actually participated and the number of smear-positive cases for rural and urban clusters. In total 63,715 adults aged ≥15 years were enumerated in the study population, of which 52,098 (81.8%) persons participated (Table 1). The mean (±S.D.) age of the participants was 35.5±15.7 years.

![Flowchart](image)

**Fig. 3. Summary of the tuberculosis prevalence survey in Bangladesh, 2007–2009.**

The eligible population in the selected clusters varied between 1403 and 2313 adults. The mean number of actual survey participants was 1302, with the participation rate varying between 57% and 92% with an average of 82% (data not shown). This relatively low participation rate is mainly due to field activities in the first six clusters. In these clusters the households were visited only once. When eligible persons were absent, no further efforts were made in recruiting them at a later stage. Instead, more households were included to reach the anticipated cluster sample of 1400 individuals. This approach resulted in an oversampling of the cluster and a subsequent low participation rate of about 60-70%. When this was observed, the procedure was changed and the field teams were instructed to visit the households...
several times before assuming the absence of an eligible individual. This reduced the number of individuals on the census list and increased the participation rate in the rest of the clusters with an average participation rate of 90%. This difference between the cluster participation rates was incorporated into the design of the individual analysis weights for the respondents.

Table 1: General characteristics of the survey population

| Characteristic | Eligible population | Participated | Did not participate |
|---------------|---------------------|--------------|---------------------|
|               | N       | %   | N       | %   | N       | %   |
| Age (yr)      |         |     |         |     |         |     |
| 0-14          | ___     | ___ | ___     | ___ | ___     | ___ |
| 15-24         | 19 132  | 30.03 | 15 275  | 29.32 | 3 857  | 33.2 |
| 25-34         | 15 108  | 23.71 | 12 446  | 23.89 | 2 662  | 22.91 |
| 35-44         | 12 293  | 19.29 | 10 195  | 19.57 | 2 098  | 18.06 |
| 45-54         | 8 177   | 12.83 | 6 803   | 13.06 | 1 374  | 11.83 |
| 55-64         | 4 920   | 7.72  | 4 081   | 7.83  | 839    | 7.22  |
| ≥ 65          | 4 085   | 6.41  | 3 298   | 6.33  | 787    | 6.77  |
| Total         | 63 715  | 100  | 52 098  | 100  | 11 617 | 100  |
| Mean ±SD*     | 35.3 ± 15.9 |     | 35.5 ± 15.7 |     | 34.7 ± 16.2 |     |
| Male          | 31 158  | 48.9 | 24 203  | 46.5 | 6 955  | 59.9 |
| Female        | 32 557  | 51.1 | 27 895  | 53.5 | 4 662  | 40.1 |
| Rural         | 31 445  | 49.4 | 26 052  | 50.0 | 5 393  | 46.4 |
| Urban         | 32 270  | 50.6 | 26 046  | 50.0 | 6 224  | 53.6 |

S.D. Standard deviation

In the survey, 33 sputum smear-positive pulmonary TB cases (SS+TB) were detected. The overall crude prevalence of smear-positive TB was therefore 63.3/100,000 population (95% CI 43.6-88.9) and the adjusted prevalence was 79.4/100,000 (95% CI 47.1-133.8) in persons aged ≥15 years. Of the 33 SS+TB cases detected, 20 (61%) were positive in two initial samples of sputum collected, 13 (39%) initially had one sample positive and had either an additional sample positive or chest X-ray positive (data not shown). A quality control process was adopted and practiced throughout the survey period. All FM positive slides were restained and examined with ZN stain on a routine basis at the field site and all positive ZN slides were re-examined at the central laboratories. No discrepancies were reported. Of the 33 smear-positive cases, 29 were also culture-positive for *Mycobacterium tuberculosis*. Of the four culture-negative cases three were diagnosed as TB cases by X-ray with one sputum positive (scanty) on both FM and ZN microscopy and one had contamination. The majority of cases (23, 79%) were found to be sensitive to all drugs and only one (3.4%) multidrug resistant (MDR) case was detected. At the time of detection, three (9.0%)
of the 33 detected cases were under DOTS treatment at a local centre and 15 (45.5%) had a history of cough of varying duration.

The crude and adjusted prevalence of SS+TB was higher in males than females and in rural rather than urban areas. The crude prevalence in males was 99.2 (95% CI 63.5-147.8) and the adjusted rate was 121.7/100,000 (95% CI 69.6-212.8), while in females the rates were 32.3 (95% CI 14.8-61.3) and 40.3 (95% CI 13.4-121.4), respectively, with a female:male ratio of 0.33. The crude and adjusted prevalence rates for the rural areas were 76.8 (95% CI 46.9-118.6) and 86.0 (95% CI 47.9-154.3), respectively, and for the urban areas the rates were 49.9 (95% CI 26.6-85.3) and 51.1 (95% CI 27.7-94.1), respectively (Table 2). The prevalence rates increased with increasing age except in the ≥65 years age group. The prevalence decreased with advancement in education in different stages with the highest prevalence in the uneducated group (138.6/100,000, 95% CI 78.4-245.0).

**Table 2:** Estimated number of sputum smear positive tuberculosis (TB) cases and prevalence in Bangladesh, 2007-2009 by age, sex, and area of residence (per 100,000)

| Characteristics | Number of TB Cases detected | Crude prevalence (95% CI) | Adjusted prevalence (95% CI) |
|-----------------|------------------------------|---------------------------|------------------------------|
| All             | 33                           | 63.3 (43.6-88.9)          | 79.4 (47.1-133.8)            |
| **Sex**         |                              |                           |                              |
| Male            | 24                           | 99.2 (63.5-147.8)         | 121.7 (69.6-212.8)           |
| Female          | 9                            | 32.3 (14.8-61.3)          | 40.3 (13.4-121.4)            |
| **Age in years**|                              |                           |                              |
| 15-24           | 5                            | 32.7 (10.7-76.4)          | 43.0 (16.2-115.0)            |
| 25-34           | 3                            | 24.1 (4.9-70.4)           | 46.4 (10.0-215.0)            |
| 35-44           | 6                            | 58.9 (21.6-128.1)         | 82.0 (36.0-187.2)            |
| 45-54           | 6                            | 36.0 (32.4-192.0)         | 99.0 (39.0-254.3)            |
| 55-64           | 7                            | 171 (69.0-354.0)          | 201.0 (96.3-418.3)           |
| 65+             | 6                            | 182.2 (67.0-397.0)        | 150.0 (53.5-418.3)           |
| **Residence**   |                              |                           |                              |
| Rural           | 20                           | 76.8 (46.9-118.6)         | 86.0 (47.9-154.3)            |
| Urban           | 13                           | 49.9 (26.6-85.3)          | 51.1 (27.7-94.1)             |
| **Education**   |                              |                           |                              |
| No education    | 15                           | 122.0 (68.2-201.1)        | 138.6 (78.4-245.0)           |
| Primary         | 8                            | 68.6 (29.6-135.2)         | 69.2 (31.2-153.6)            |
| Secondary       | 6                            | 35.0 (12.8-76.0)          | 51.8 (22.6-118.6)            |
| Secondary +     | 4                            | 36.5 (9.9-93.3)           | 39.3 (9.4-133.8)             |

CI, Confidence interval
Discussion

This survey is the first nationwide representative survey to determine the prevalence of smear-positive TB since the introduction of the DOTS programme in Bangladesh in 1993. The survey found a significantly lower prevalence of sputum-positive TB compared to previous surveys. The survey estimate is in agreement with a regional survey conducted in the rural area of Matlab upazila where the prevalence was reported to be 95/100,000 adult population. However, the prevalence rate was much lower in a survey conducted in another area by the Damien Foundation where the overall prevalence of smear-positive TB was only 24/100,000. Both the surveys screened for suspected TB cases and then collected specimens from them for microscopy. The surveys varied in their sampling techniques, including population and content of the screening interview. The survey results showed a much lower prevalence than the recent WHO estimate of 142/100,000 in all age groups. The WHO estimate is based on a limited tuberculin survey conducted in 1960 and on routine case notification data. Given the weaknesses in routine surveillance and notification of TB in Bangladesh, the WHO estimate has marked uncertainties. Results from the population-based prevalence survey of smear-positive TB other countries revealed higher rates in Viet Nam (196.8/100,000) and Eritrea (90/100,000) than in Bangladesh.

The prevalence was found to be higher in the rural population (86.0/100,000) compared to urban (51.1/100,000). Similar findings have been observed in the Viet Nam survey. In Bangladesh urban areas are densely populated and about one third of the population lives in crowded slums. A lower number of cases in urban areas was also notified in the NTP in 2009. In 2009, the NTP notified a total of 151,062 of all forms of TB cases (104/100,000 population) nationwide, of these 17.7% were reported from urban areas. The urban areas of Bangladesh currently contain about 30% of the total population and are characterized by high mobility and internal migration. The DOTS coverage started later and was less organized than in the rural areas. Of note, in urban areas health service delivery is pluralistic in nature with the presence of a large number of primary, secondary to tertiary public and private health centres as well as qualified and non-qualified private practitioners. There has been intensified advocacy, communication and social mobilization (ACSM) activities for TB control nationwide over the last few years which might have impacted health-seeking behaviours in the urban population. Further, the urban population included in the study could have been more affluent (since few individuals from the slum population were included randomly in the survey).
compared to the rural population. The interaction of all these factors might be the reasons for lower prevalence of SS+TB in urban areas compared to rural areas.

In this survey the prevalence of TB in males was threefold higher compared to females. The findings are consistent with routine case findings and with local sporadic surveys conducted by different organizations. Since 1993 a higher male:female ratio has also been found consistently in notified cases in the NTP, except for the <14 years age group. The higher prevalence in the elderly age group is probably an indication of shifting of infection pattern and transition of disease prevalence. Since 2006, the average age of suspect cases examined was >35 years in the NTP. This also indicates a shift in age. Moreover, about 60% of new SS+cases notified to the NTP in 2009 were in this age group. The inverse relationship of TB prevalence which was highest in uneducated persons, as noted in our survey, is probably related distally with knowledge, stigma, poverty, and health-seeking behaviour in TB cases.

In our survey the decision to adopt the approach of collecting specimens from all individuals was made primarily for logistical reasons. Moreover, guidelines for conducting TB prevalence surveys were not available at the time the survey was planned. Considering the availability of infrastructure facilities and other support the chosen strategy was found to be a feasible and affordable approach for the survey. All eligible individuals were asked to provide two sputum samples for smear microscopy. Theoretically this would provide the best estimate for smear positivity in the population because nobody was excluded from examination. The strategy applied in Bangladesh had already been tested in Eretria. The applied approach might have limitations if the participation rate is not adequate, the quality of the collected specimens is poor, consistent and standard field and laboratory procedures are not maintained, and microscopy is conducted poorly. In this survey, even though we had lower participation in a few early clusters (60-70%), this was soon corrected to >90% in the rest of the clusters. Standard sputum collection methods were applied throughout the survey. No specimens were rejected based on macroscopic aspects and rigid quality control measures were applied.

Initial smear microscopy was performed using FM because this technique allows for a more rapid assessment of the specimen. It has at least the same sensitivity and specificity as conventional ZN microscopy - estimated to be between 52% and 97%. Furthermore, FM is assumed to perform better than ZN microscopy in identifying paucibacillary specimens. Similarly, a sample (2.5%) of negative slides was re-
examined and no false-negative results were reported. Considering the low sensitivity of the sputum microscopy the underestimation and uncertainty of our estimate might be greater. Assuming 75% sensitivity of the fluorescence and with no false-negative results reported in the field, the prevalence of smear-positive TB might be as high as 105/100,000 (95% CI 79-137) population aged ≥15 years.

In our study >50% of sputum smear-positive cases did not have any symptoms of cough. The survey did not use cough as a screening criterion for inclusion. These cases would have been missed and the prevalence underestimated, if cough had been used as a screening criterion. Another approach for the prevalence survey was screening of individuals using chest X-ray, which may miss some cases as not all SS+TB cases show abnormalities on chest X-ray at any given time point. Similarly first screening for suspects based on chest symptoms might also result in missing mildly symptomatic and asymptomatic cases. In this survey we observed that about half of the detected cases did not report cough at the time of the survey. Further, only three cases were under DOTS at the time of survey indicating most cases were unknown to DOTS. Similar findings have also been reported from Viet Nam. This would have resulted in a serious underestimation of prevalence if this strategy had been adopted. Screening using a combination of chest X-rays and symptoms, the method advocated by WHO for TB prevalence surveys, is costly and needs much expertise in the field. Adopting this strategy produced an overestimation in Viet Nam.

Some limitations of the study should be noted. The study did not cover the population aged 0-14 years which makes it difficult to calculate prevalence in the whole population. There is a paucity of TB data for Bangladeshi children and sputum samples are rarely available from children. Moreover, workplace areas, prisons and other institutionalized populations were not covered. The overall sampling strategy selected 20 urban/semi-urban and 20 rural clusters regardless of the underlying population in rural and urban areas. This disproportionate sampling in the two groups was corrected during the analysis by including a stratification factor in the overall weighing of participants. This resulted in a valid estimate of the denominators used in the calculations, but a loss of statistical power due to inefficient sampling reflected in a wide interval around the estimate. The statistical power was also negatively influenced by the small number of identified cases which was reflected in the overall design effect of 2.7. Due to logistical reasons only 2.5% of the negative slides were rechecked. This leaves the possibility for ascertainment bias in the survey leading to a possible underreporting of smear-positive TB cases.
Further, there was no culture performed on smear-negative cases which precludes assessment of the prevalence of bacteriologically confirmed TB.

Despite the limitations and logistic constraints, the survey has produced a valid and reliable estimate of the prevalence of smear-positive TB in the population aged ≥15 years. It has highlighted the higher prevalence in rural areas and aged population, and a disproportionate distribution in the male and female population. The TB control programme in Bangladesh has achieved good coverage of case detection and treatment success rates over the past few years, but the present findings warrant intensified TB control activities be continued, with increased emphasis given to older people and the rural population of the country. It is recommended that control surveys are conducted at regular intervals in order to monitor the TB situation in Bangladesh.

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CHAPTER 3

TUBERCULIN SURVEY IN BANGLADESH, 2007-2009: PREVALENCE OF TUBERCULOUS INFECTION AND IMPLICATIONS FOR TB CONTROL

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Summary

Objectives: To assess the prevalence of tuberculous infection and the annual risk of tuberculous infection (ARTI) for 2007–2009 in Bangladesh, approximately 45 years after the first tuberculin survey in 1964–1966.

Methods: A tuberculin survey was conducted along with the National Tuberculosis Disease Prevalence Survey in 2007–2009. This was a multistaged community-based, cross-sectional survey, including 17718 children aged 5–14 years. The prevalence of tuberculous infection was estimated using the mixture method and a cutoff point of ≥8 mm.

Results: The prevalence of infection was 10.0% (inter-quartile range [IQR] 8.6–12.2) in children aged 5–9 years and 17.9% (IQR 15.4–20.2) in those aged 10–14 years using the mixture analysis. Prevalence was 12.4% (95% confidence interval [CI] 11.7–13.1) in children aged 5–9 years and 22.6% (95%CI 21.6–23.4) in those aged 10–14 years using a cut-off point of ≥8 mm. The estimated ARTI was respectively 1.5% and 1.7% in 5–9 and 10–14 year olds using the mixture method and respectively 1.9% and 2.1% using the cut-off method.

Conclusions: The moderate reduction in the prevalence of infection and slow decline of the ARTI after two decades of DOTS implementation indicates considerable ongoing transmission.

Key Words: community-based; tuberculous infection; annual risk; tuberculin skin test; Bangladesh
The Prevalence of *Mycobacterium tuberculosis* infection is an indicator for tuberculosis (TB) transmission in a community and may be used to monitor the burden of disease. Knowledge of the TB burden and its trends is imprecise in Bangladesh. The prevalence of smear-positive cases was reported in two TB prevalence surveys at 318 per 100,000 population in 1964–1966 and 910/100,000 in 1987–1988. The recently conducted 2007–2009 National Tuberculosis Prevalence Survey (NTPS) reported a markedly decreased prevalence of 79.4 smear-positive cases/100,000 in those aged ≥15 years.

The causes of the decline in TB prevalence may be the result of successful TB control, socio-economic development or concurrent development in other non-health sectors. Cure rates in the National Tuberculosis Programme (NTP) increased from 75% in 1993–1995 to >90% in 2011, while the gross domestic product per capita increased from US$594 in 1994 to US$1584 in 2010.

As the NTP wished to examine whether the decline in TB prevalence was accompanied by a similar decline in the risk of *M. tuberculosis* infection, a national tuberculin survey was embedded in the latest NTPS. The only national tuberculin survey conducted in Bangladesh was in 1964–1966. A reassessment of the survey data revealed some methodological problems, making the results for the 5–9 years age group questionable. These included the probability of reduced sensitivity in children aged 5–9 years due to lower age and the low doses of antigen used (1 tuberculin unit [TU]), not reaching some of the remote areas, and the inability to read tested persons in some instances.

In this article, we report the results of the 2007–2009 tuberculin survey. The results will provide an estimate of the annual risk of tuberculous infection (ARTI) following countrywide implementation of the DOTS strategy in the 1990s.

**Materials and Methods**

**Setting**

The survey was conducted by the Bangladesh NTP in collaboration with the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), with the support of the World Health Organization (WHO) and the KNCV Tuberculosis Foundation. As in the 1964–1966 survey, we included children aged 5–14 years. School attendance for children aged ≥12 years (secondary school) is considerably lower than for younger children in Bangladesh, with greater drop-out rates between
primary and secondary schools among girls than among boys. For this reason, we conducted a community-based survey to avoid the bias likely in a school-based survey.

**Design**

The survey was carried out in children from 20 urban and 20 rural clusters. Stratified cluster sampling (by urban/rural) was performed, with sub-districts being selected with probability proportional to population size. A *mauza* or *muhallah* (smaller geographical units) from each sub-district was then selected by simple random sampling. In each cluster, inclusion of households started with random selection of an initial household after which other households were added consecutively following a pre-defined direction until the required sample size was achieved. The selected households were visited several times to include as many eligible children as possible.

The sample size was calculated on the basis of an assumed decline in infection prevalence in children aged 5–9 years from 4.1% to 2.5% between 1964 and the current survey, and from 13.6% to 10% in those aged 10–14 years. With an anticipated participation rate of 90%, a design effect of 3, a significance level of $P < 0.05$ and a power of 90%, the survey required a total study population of around 15,000. Given the operational context of the NTPS of which this tuberculin survey was a part, we anticipated that 500 children per cluster would be available from the same households, giving a total sample size of 20,000.

**Skin testing survey**

All children aged 5–14 years who were resident in the selected households were eligible for inclusion. Only children whose legal guardians provided written informed consent were included. Children who were severely ill, mentally retarded, those with a history of convulsion or who had severe skin rashes were excluded.

Inclusion of the children started at the first household of the cluster and ended with the inclusion of all the children of the household in which the 500th child lived. After enrolment, bacille Calmette-Guérin (BCG) status was checked and children were tested using intradermal administration of 0.1 ml of tuberculin containing 2 TU of purified protein derivative RT23 with Tween 80 (Statens Serum Institute, Copenhagen, Denmark) in the ventral aspect of the left forearm, regardless of BCG status. Skin reactions were read after 72 h using a transparent ruler. Children who
had been administered tuberculin but were not present for reading were traced and examined on the following day.

Parents were informed of the results and advised if any measures were necessary. All children with indurations of $\geq 15$ mm were referred to the nearest diagnostic centre for clinical evaluation and management per NTP protocol.¹⁶

**Quality control of tuberculin testing**

The design of the tuberculin survey followed the standard guidelines of the WHO/International Union Against Tuberculosis and Lung Disease for conducting tuberculin skin test (TST) surveys in high-prevalence countries.¹,¹⁵ Tuberculin testers received training by two international tuberculin reference nurses. Several refresher and on-the-job training courses were carried out to maintain adequate standards. A random sample of the children was read a second time by another tuberculin reader blinded to the initial results. If serious discordances were identified by the double reading, additional training in the reading of tuberculin results was provided.

The survey protocol was approved by the research review and ethical review committees of the icddr,b. The protocol, along with the NTPS, was approved by the Ministry of Health and Family Welfare of the Government of the Peoples’ Republic of Bangladesh.

**Statistical analysis**

This protocol followed recent recommendations to include all children,¹⁵,¹⁷ irrespective of BCG status, for analysis. An initial frequency distribution was drawn to identify digit preference or any other distribution pattern. Data were smoothed by applying a moving average of five.

We used a mixture analysis for the study. We also explored the prevalence of tuberculous infection with a fixed cut-off point indicated by the graphic distribution obtained from the initial mixture analysis. The mixture method disentangled the overall distribution of the TST reaction sizes used in the cut-off method into separate distributions due to *M. tuberculosis*, non-specific causes (other mycobacterium, BCG) and non-infected individuals.¹⁸ This allowed for a more precise estimate of the prevalence of infection by *M. tuberculosis*. The method is not new and had been successfully used in the analysis of previous TST surveys. It is a Bayesian Markov Chain Monte Carlo simulation approach which calculates a posterior distribution of
the prevalence of tuberculous infection with its associated interquartile ranges (IQRs). The cut-off method provided a single prevalence estimate with associated confidence intervals (CIs).

We assessed the fit of three parametric models (normal, log-normal and Weibull) to describe *M. tuberculosis* infection, and two models (log-normal and Weibull) to describe distribution among non-infected children. A model fit for each of the six possible combination models was assessed by examining maximum log-likelihood values, percentage of predictive failures and analysis of the graphical distributions of reactions. From the graphs produced by the distribution of indurations, a fixed cut-off point was chosen to estimate the prevalence of tuberculous infection using the conventional cut-off method. ARTI was estimated according to the following formula: \( \text{ARTI} = 1 - (1 - \text{prevalence})^{(1/\text{average age})} \).

In secondary analyses, we explored the relationship between tuberculin indurations and the socioeconomic position (SEP) of the household, and between tuberculin indurations and exposure to an adult with TB in the same household. SEP was assessed by validated asset items for each of the households included in the latest NTPS. A principal component analysis generated household scores and these were categorised in tertiles. Children belonging to a particular household were attributed the assets of that household. Details of the method used is described elsewhere.

Data analysis was performed using the statistical package Stata, v. 10.0 (Stata Corp, College Station, TX, USA), and software ‘R’, version 2.4 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

Of 22,309 children included in the survey, 20,285 were eligible for the study. Among the children eligible, 2103 (10.4%) were absent and 364 (1.8%) refused or were excluded. A total of 17,718 (87.3%) children were included as study participants. There were no marked differences between those analysed and those who were not with respect to sex, age group, setting, SEP or exposure to TB in the household (data not shown). All study participants were tested with tuberculin, and almost all of them (99.3%) were read for reaction sizes. BCG scars were present in >85% of children, irrespective of age (Table 1).
Table 1: Participation and test status of children, 2007-2009 tuberculin survey, Bangladesh

| Study population      | Children aged 5-9 years | Children aged 10-14 years |
|-----------------------|-------------------------|--------------------------|
| Children in census    | 11782                   | 10527                    |
| Eligible children     | 10651                   | 9634                     |
| Absent                | 1025                    | 1078                     |
| Refused               | 70                      | 64                       |
| Excluded              | 128                     | 102                      |
| Children tested       | 9428                    | 8290                     |
| Children read among   |                         |                          |
| those tested, n(%)    | 9357 (99.2)             | 8228 (99.3)              |

The percentage of non-reactors (indurations = 0) was 76.6% in those aged 5–9 years, and 63.1% in those aged 10–14 years. More than 50% of the reactors in the 5–9 years age group and 46% in the 10–14 years age group had indurations of between 1 and 8 mm (Figure 1).

Fig. 1: Frequency distribution of reaction sizes in children 5-9 and 10-14 years, Bangladesh, 2007-09 tuberculin survey. Proportion of children with indurations, %. Distribution after smoothing on five averages. All reactions of ‘0’ mm have been omitted for clarity, which was 76.6% in children aged 5-9 years and 63.1% in those aged 10-14 years.
There were few predictive failures in any of the combinations in the mixture analysis; combinations did not differ much in their maximum log-likelihood estimates. Among all combinations, the ln/ln graph showed a modest bimodal distribution with an anti-mode at 8 mm (Figure 2). This cut-off point was used for analysis based on the conventional fixed cut-off point approach.

Applying the mixture method, the prevalence of tuberculous infection was respectively 10.0% (IQR 8.6–12.2) and 17.9% (IQR 15.4–20.2) in those aged 5–9 years and 10–14 years. Using a cut-off point of ≥ 8 mm, the prevalence of tuberculous infection was respectively 12.4% (95%CI 11.7–13.1) and 22.6% (95%CI 21.6–23.4) in those aged 5–9 years and 10–14 years. The estimated ARTI for 5–9 years was 1.5%, while for the 10–14 years age group it was 1.7% using the mixture method. This was respectively 1.9% and 2.1% for both age groups using the fixed cut-off point at ≥ 8 mm (Table 2).
**Table 2:** Prevalence of infection and ARTI, 2007-2009, tuberculin survey, Bangladesh

|                      | Children aged 5-9 yrs |         | Children aged 10-14 yrs |         |
|----------------------|------------------------|---------|-------------------------|---------|
|                      | Prevalence of infection| ARTI %  | Prevalence of infection  | ARTI %  |
| Mixture Method, % (IQR) | 10.0 (8.6-12.2)        | 1.5     | 17.9 (15.4-20.2)        | 1.7     |
| Cut-off at ≥8 mm, % (95% CI) | 12.4 (11.7-13.1)  | 1.9     | 22.6 (21.6-23.4)        | 2.1     |

ARTI = annual risk of tuberculous infection, IQR = interquartile range, CI = confidence interval.

The 2007–2009 survey identified only 33 new smear-positive pulmonary TB cases. Nineteen children were from households where a TB case was diagnosed during the survey and were considered exposed to a TB case. Among the children with exposure to a TB case, 9 (47.4%) had indurations of ≥8 mm compared to 2934 (16.7%) children without exposure to a TB case (odds ratio [OR] 4.5, 95% CI 1.7–11.9; Table 3).

**Table 3:** Potential risk factors for infection: within-household exposure status and indurations, asset status and indurations

|                      | < 8 mm n (%) | ≥ 8 mm n (%) | All n (%) |
|----------------------|-------------|-------------|-----------|
| Exposed*             | 10 (52.6)   | 9 (47.4)†   | 19 (0.11) |
| Not exposed          | 14 596 (83.3) | 2934 (16.7) | 17 530 (99.9) |
| All                  | 14 606 (83.2) | 2943 (16.8) | 17 549 (100.0) |
| Asset status‡        |             |             |           |
| Lower                | 4552 (84.2)  | 851 (15.8)  | 5403 (30.8) |
| Middle               | 4842 (82.8)  | 1006 (17.2) | 5848 (33.3) |
| Upper                | 5212 (82.8)  | 1086 (17.2) | 6298 (35.9) |
| All                  | 14 606 (83.2) | 2943 (16.8) | 17 549 (100)  |

*Children from a household where a smear-positive TB case was detected during 2007-2009 survey.
†P < 0.000
‡P = 0.055

Among the children belonging to the lower SEP tertiles, 15.8% had indurations of ≥8 mm compared to 17.2% in both the middle and upper SEP tertiles. The prevalence of tuberculous infection was not significantly associated with any of the SEP tertiles (Table 3).
Discussion

This tuberculin survey was conducted nearly 45 years after the first survey carried out in 1964–1966. There is therefore only limited information available to put this estimate into context. The 1964–1966 survey provided valid data only for the 10–14 years age group using the cut-off method with an 8-mm threshold. The prevalence of tuberculous infection was 34.4%. The new prevalence of tuberculous infection in the same age group using the same methodology was 22.6%, showing an average decline of nearly 1% between the two surveys. This indicates that despite the efforts of the NTP, there has been little improvement in curbing the risk of tuberculous infection in the community since 1964.

This is in sharp contrast with the reported decline in the prevalence of smear-positive TB in the community, from 318/100,000 in 1964–1966 to only 79.4/100,000 in 2007–2009, an annual decline of approximately 3.2%. A lower prevalence of infectious TB patients reduces TB transmission within the community, which should be reflected in a decline in the prevalence of tuberculous infection. Ascertaining the reasons why this has not been observed in Bangladesh is challenging.

We have shown earlier that the NTP does not have adequate coverage among the poorer population groups of Bangladesh. Higher TB prevalence among the poor, combined with delays in care seeking and treatment, may create a favourable environment for transmission. Our results, however, do not show any association between the prevalence of tuberculous infection and SEP, although they indicate a clear relationship between induration size and TB exposure. This would suggest that TB transmission in our study was not influenced by SEP. However, our methods of data capture (for either SEP or prevalence of infection) might not be strong enough to establish such an association.

SEP distribution in the survey population was based on an asset score, which provided a relative classification of SEP rather than an absolute measure. Although the distribution of assets-based SEP was homogeneous in relation to the underlying absolute SEP, the method was insufficiently sensitive to detect a relationship between the SEP and the prevalence of tuberculous infection. Data on the relationship between tuberculous infection and SEP were not unanimous, despite the obvious link given the higher prevalence of TB in this setting. In South Africa, Mahomed et al. reported that low income and low education levels (factors strongly associated with SEP) increased the risk of latent tuberculous infection. In contrast,
Boccia et al. showed that in Zambia the risk of tuberculous infection was associated with a higher SEP.24

The ability of a tuberculin survey to measure the prevalence of tuberculous infection might be questionable in itself, given the well-known limitations in design and analysis.19 We used a strict quality control strategy comprising training, monitoring and retraining to obtain high-quality data. Analyses were performed after smoothing of the data, and the mixture method was used instead of the crude cut-off approach. This strategy minimised the methodological problems seen in tuberculin surveys as much as possible. Problems with TST measurements and analysis can probably be overcome by using interferon-gamma release assays (IGRAs) as an alternative to TST, not only for their high specificity but also because the results are not affected by BCG vaccination status,25,26 although IGRAs are costly and technically challenging in low-resource settings.17

The limited decline in ARTI or prevalence of tuberculous infection in Bangladesh in this study should be interpreted with caution, as not only were the two tuberculin surveys conducted 45 years apart, they differed methodologically with respect to sampling and the use of reagents for testing (1 TU instead of 2 TU);4 also, considerable societal and programmatic changes have occurred in the intervening period. Despite this, the current study provides the first estimate of the prevalence of tuberculous infection after the nationwide implementation of the DOTS strategy. As such, it can serve as an important starting point for further studies. Despite the limitations of tuberculin surveys, multiple surveys with identical methodology in an appropriate time frame have been shown to provide information on trends.18,27,28 Assessing the association between SEP and the risk of tuberculous infection should be conducted in specifically designed studies to ensure maximum power and attribution. Such studies will be of benefit to the Bangladesh NTP in designing interventions for effective TB control.

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CHAPTER 4

SOCIO ECONOMIC POSITION IN TB PREVALENCE AND ACCESS TO SERVICES: RESULTS FROM A POPULATION PREVALENCE SURVEY AND A FACILITY-BASED SURVEY IN BANGLADESH

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Abstract

Background: In Bangladesh DOTS has been provided free of charge since 1993, yet information on access to TB services by different population group is not well documented. The objective of this study was to assess and compare the socioeconomic position (SEP) of actively detected cases from the community and the cases being routinely detected under National Tuberculosis Control Programme (NTP) in Bangladesh.

Methods and Findings: SEP was assessed by validated asset item for each of the 21,427 households included in the national tuberculosis prevalence survey 2007–2009. A principal component analysis generated household scores and categorized in quartiles. The distribution of 33 actively identified cases was compared with the 240 NTP cases over the identical SEP quartiles to evaluate access to TB services by different groups of the population. The population prevalence of tuberculosis was 5 times higher in the lowest quartiles of population (95.4, 95% CI: 48.0–189.7) to highest quartile population (19.5, 95% CI: 6.9–55.0). Among the 33 cases detected during survey, 25 (75.8%) were from lower two quartiles, and the rest 8 (24.3%) were from upper two quartiles. Among TB cases detected passively under NTP, more than half of them 137 (57.1%) were from uppermost two quartiles, 98 (41%) from the second quartile, and 5 (2%) in the lowest quartile of the population. This distribution is not affected when adjusted for other factors or interactions among them.

Conclusions: The findings indicate that despite availability free of charge, DOTS is not equally accessed by the poorer sections of the population. However, these figures should be interpreted with caution since there is a need for additional studies that assess in-depth poverty indicators and its determinants in relation to access of the TB services provided in Bangladesh.
Introduction

The association between tuberculosis (TB) and poverty is well documented. Several studies and reviews concluded that poverty not only exposes a person to more TB infection\(^1\)-\(^8\) but also influences all aspects of the TB disease process.\(^9\)-\(^12\) It has been documented that poverty is associated with delayed care seeking,\(^13\),\(^14\) late diagnosis,\(^13\),\(^15\) progression of the disease,\(^16\) delayed initiation of treatment,\(^13\),\(^16\) and inadequate follow up.\(^17\)-\(^19\) It is also noted that poverty leads to poor adherence to treatment, more complications and poor treatment outcomes like default from treatment.\(^2\),\(^8\),\(^20\)-\(^23\)

On the other hand, TB disease itself induces many consequences and makes the poor poorer. As a result of poverty-related physical illness, extensive malnutrition and subsequent decreased host resistance the poor are likely to have more extensive and severe forms of TB disease and run higher risks of poor treatment outcomes.\(^20\)-\(^23\) Evidence indicates that the damaging effects of TB are catastrophic to those who were relatively poor or marginalized before being infected with TB. TB subsequently pushes the income insolvent into poverty, the food deprived into a condition of further malnutrition.\(^5\),\(^11\),\(^23\),\(^24\) The long course of the disease and treatment make the poor socially vulnerable and deprived and locks them in the poverty stricken condition. The poor suffers more from TB, and TB puts the poor in more vulnerable state.\(^23\),\(^25\) In fact, Poverty and TB are locked in a vicious cycle, as one triggers the other.

One of the reasons of providing diagnosis and treatment free of cost is that everyone with the disease can access treatment when needed particularly the poorer section of the population. But even after nearly 15 years of Directly Observed Treatment, Short course (DOTS) implementation, the global figure does not support this assumption. The World Health Organization (WHO) has reported the global burden of TB as 8.8 million incident cases in 2010,\(^26\) 82% of them are from 22 high burden countries, categorized mostly as low income countries. With a global case detection rate of 65% for all forms of TB, this means that a marked proportion of these cases did not have any access to quality diagnosis and care. In Bangladesh in 2010 a total of 153,892 new cases were identified, with an estimated case detection rate of just 46% for all cases and 70% for new smear-positive cases. More than 80% of the identified TB cases were from rural areas.\(^26\)-\(^28\)

In 2011, Bangladesh was one of the 22 high TB burden countries, having an estimated prevalence of 411 (188–671)/100,000 population.\(^26\) Bangladesh has made
considerable progress in DOTS implementation since its adaptation in 1993. The country achieved a 100% DOTS coverage in 2003, the treatment success rate is persistently above 90% from 2000, and case detection rate for new smear positive pulmonary TB above 70% since 2006. Despite all these successes, evidence on health care utilization, particularly accessing DOTS by socioeconomic groups is scarce. Case notification data segregated by socio economic strata is not available, but inequity in accessing services in other sectors of the health services suggests that inequity in service utilization might also be a challenging issue for the TB control programme. Such information is needed to improve the implementation and coverage of National Tuberculosis Control Programme (NTP) Bangladesh in more effective and equitable ways. It has been recognized that TB control needs to focus beyond therapeutic strategies to include poverty and tackling the social determinants of TB. National programmes are urged to adopt strategies to address these issues by actively identifying poor and vulnerable populations and facilitate access to diagnosis and treatment to them.

In the recently conducted national TB prevalence survey in Bangladesh, emphasis therefore had been given to collect information on socio economic position (SEP) of the participants and the TB cases detected in order to assess the relationship between SEP and TB in the country. To assess whether the NTP actually reaches the lower echelons with regards to SEP in the population, we concurrently assessed the SEP from TB cases passively detected by the NTP, and the cases detected actively under a prevalence survey.

**Methods**

Prevalent TB cases were derived from the national tuberculosis prevalence survey carried out between 2007 and 2009. The objective of this survey was to assess the prevalence of smear-positive TB in Bangladesh. This was a multi stage community based cluster survey including 40 randomly selected clusters, 20 from rural and 20 from urban areas throughout the country. The reason for including equal numbers of clusters from both rural and urban areas was a programmatic decision. It was deemed strategically not wise to put more focus on rural areas than on urban areas, given the large number of stakeholders within TB-control activities in Bangladesh. By including equal number of clusters, we could satisfy all of these stakeholders. From the start we knew that this decision would mean that we had to adjust for unequal sampling probabilities in the analysis, as we did. By including appropriate weights to each included individual, the study population became representative for
the target population at large. The methodology is therefore valid, albeit not statistically efficient.

The sample size in the survey was based on the assumption that the prevalence of smear-positive pulmonary TB cases varied between 100 and 200 per 100,000 population. It was therefore expected to identify 50 to 100 cases in a sample of 50,000 individuals, or on average 2 cases per cluster. About 52,000 persons ≥15 years of age from 21,427 randomly selected households participated in the survey. A detailed description on methods and sample size was published elsewhere. Socioeconomic information was collected from all these households with the household heads being most often the main responders.

We considered an ideal ratio of cases versus controls at 1:4, which would mean including 8 passively identified cases per cluster. Given the limited time in the cluster this was deemed not feasible, we therefore reduced the ratio to 1:3 and included 6 controls per cluster, giving rise to 240 cases passively detected under NTP.

Routinely diagnosed TB cases or passively detected control cases were obtained from the most recent registered TB patients in the sub-district TB diagnostic centre of the selected survey clusters. These patients were newly detected smear-positive cases currently under any phases of treatment at a given point of time. The DOTS centers represent the only available place for TB treatment and care under the national programmes in the selected district. The selected patients are therefore a valid representation of passively identified TB cases in the country.

**Outcome Measures: SEP Measurement**

Socioeconomic position was estimated by determination of a household asset score based upon ownership of consumer items including home utensils (such as television, bicycle etc.), utilities in home (Bed, Wardrobes), and dwelling characteristics (source of drinking water, sanitation facilities, building materials), that are related to wealth status. Assets were assessed by questionnaire or by direct inspection. The assets score methodology, a composite wealth index, used in this study was developed and tested by the World Bank through the Demographic Surveillance system (DHS), and is used in many countries, including Bangladesh, to estimate inequities in household economic condition, service utilization and health outcomes.
To calculate the assets score, each asset item was noted as present or absent from the household. This information was included in a principal component analysis to derive at the weights to be applied to each variable within the calculation of the overall assets score. We used the first principal component only since this account for the maximum possible variability in the data. With each asset assigned a weight, we calculated for each household the assets score based on the presence of assets, in such a way that the overall distribution of assets scores had a mean equals to zero.

The final assets list was reduced from initial 31 to 17 after a careful selection process. We deleted the assets that were present in very small (<20%) or very large number of households (>80%) because they would not provide much discriminatory power to the analysis. We also deleted those assets that had more than 10% missing values because inclusion could lead to skewing of the data. We preferred this over deletion of assets based on a low weight of the asset in the analysis because is less data drive.

We then deleted the few assets that can be seen as a proxy for urban area: that turned out to be “piped water in the house”, “piped water outside house” and “has motorcycle”. The urban effect was additionally addressed by including the urban/rural variable into the multivariable model assessing case detection by SEP.

We did not exclude assets with a potential direct health effect, because we were not assessing the risk of TB in multivariable analysis. Therefore there was not fear of including such an effect twice (as an asset and as a direct risk factor).

A single asset score was developed for all sample households from the rural and urban population. Within the setting of a prevalence survey, the assets score methodology is the recommended approach to incorporate measures of SEP without jeopardizing overall survey objectives. The information of SEP within the survey population was collected during the houseto-house census at the start of the survey. Routinely identified TB patients from the diagnostic centers were visited at their home to obtain this information. The total distribution of assets scores was divided into quartiles from one (lowest) to four (highest). The grouping of households into broad socio economic categories is mostly conventional, based on assumption that SEP is uniformly distributed but occasionally could be data driven. Using quartiles provided the best representation of the relationship between SEP in the study, as tertiles showed marked clumping of cases in the middle category, and quintiles provided difficulties for the small number of actively detected cases in the survey. Also, interpretation of data in quartiles is straightforward with the four categories splitting equally into two groups of upper and lower SEP.
Sputum positive tuberculosis was measured by direct sputum smear microscopy of at least two sputum samples from all participants regardless of symptoms, using fluorescence microscopy at field level laboratories. In line with the national algorithm, TB was diagnosed when two sputum samples were smear positive, or when one sample was smear positive with in addition a chest X-ray suspected of TB.

**Analytical Approach**

Data was entered and analyzed using Stata statistical software (Release 10.0, Stata Corporation, College station, TX USA). TB prevalence estimates were based on an adjusted weighted analysis taking into account the survey design and attrition in the survey, using complex survey analyses techniques. Prevalence of TB was stratified by quartiles of SEP in the total survey population. The SEP of TB cases identified in the survey and those identified by the NTP was projected on the quartiles of SEP form the general population for comparison.

The SEP distribution of the survey cases and the NTP cases was compared using a logistic regression approach in which the outcome variable was defined as “low SEP”. A case was considered to have a low SEP when the household SEP was classified as being in the lowest 2 quartiles. Explanatory variable were age (dichotomized at 45 years), sex, urban/rural setting, and type of case (survey or NTP). A p-value <0.05 was considered statistically significant for main effects, while p<0.1 was used for interaction terms.

**Ethical Approval**

This study was approved by the ministry of health and family welfare of Bangladesh, the Research Review Committee (RRC) and Ethical Review Committee (ERC) of the icddr,b, a multi disciplinary international research institution situated in Dhaka, Bangladesh. Written informed consent was received from all participants.

**Results**

A total 21,427 households were included in the survey, equally from 10,688 (49.8%) rural and 10,739 (50.2%) urban areas. In total 52,098 adults ≥15 years participated in the survey of which 27,895 (54%) were female. About three quarter (73%) of the survey participants was between 15–44 years of age, 23.6% had no education, and 41% were house wives. The major categories of occupation included agriculture related works (8.8%), employed in the non-agriculture sector works (fishermen, Manual laborer etc.) (14.7%), sales and services (vendors, shops, small business etc.) (18.2%) and Dependent and others (including housewives) (58.3%) (Table 1).
Table 1: General characteristics of the participants and the cases detected in the survey and under NTP at the time of survey 2007-2009

| Characteristics                | Survey population n (%) | TB cases under survey n (%) | TB cases under NTP n (%) |
|-------------------------------|-------------------------|-----------------------------|--------------------------|
| Age in years                  |                         |                             |                          |
| 15-24                         | 15275 (29.3)            | 5 (15.2)                    | 62 (25.8)                |
| 25-34                         | 12446 (23.9)            | 3 (9.1)                     | 50 (20.8)                |
| 35-44                         | 10195 (19.6)            | 6 (18.2)                    | 43 (17.9)                |
| 45-54                         | 6803 (13.1)             | 6 (18.2)                    | 32 (13.3)                |
| 55-64                         | 4081 (7.8)              | 7 (21.2)                    | 30 (12.5)                |
| 65+                           | 3298 (6.3)              | 6 (18.2)                    | 23 (9.6)                 |
| Sex                           |                         |                             |                          |
| Male                          | 24203 (46.5)            | 24 (72.7)                   | 152 (63.3)               |
| Female                        | 27895 (53.5)            | 9 (27.3)                    | 88 (36.7)                |
| Residence                     |                         |                             |                          |
| Rural                         | 26052 (50.0)            | 20 (60.6)                   | 120 (50.0)               |
| Urban                         | 26046 (50.0)            | 13 (39.4)                   | 120 (50.0)               |
| Education in schooling years  |                         |                             |                          |
| 0                             | 12300 (23.6)            | 15 (45.5)                   | 55 (22.9)                |
| 1-5                           | 11657 (22.4)            | 8 (24.2)                    | 65 (27.1)                |
| 6-10                          | 17169 (33.0)            | 6 (18.2)                    | 62 (25.8)                |
| 11+                           | 10972 (21.1)            | 4 (12.1)                    | 58 (24.2)                |
| Occupation                    |                         |                             |                          |
| Agri worker                   | 4605 (8.8)              | 4 (12.1)                    | 33 (13.8)                |
| Non Agri Worker               | 7652 (14.7)             | 14 (42.4)                   | 75 (31.3)                |
| Sales and Service             | 9456 (18.2)             | 6 (18.2)                    | 109 (45.4)               |
| Dependents and others         |                         |                             |                          |
| (Including housewives)        | 30385 (58.3)            | 9 (27.3)                    | 23 (9.6)                 |

Thirty three new smear positive TB cases were detected in the survey population. Of these, 24 (73%) were male, and 20 (61%) were from rural areas. TB cases from the survey were more from middle to senior age groups of 35 to 65 (19 cases). Nearly half of these TB cases (45%) reported not to have any formal education and most of them were engaged in non-agriculture sector works (42%). TB cases detected routinely under NTP were more likely to be male 152 (63%), as was also seen in TB cases identified in the survey. In contrast to the TB cases detected in the survey, routine cases were in general from the lower age group of 15–44 years (155; 64.6%), distributed among education categories from no education (23%) to secondary or more education (50%) and most of them were engaged in non-agriculture related works (31.3%) or in sales and services (45.4%) (Table 1).
The adjusted overall prevalence of smear positive TB was 79.4 (95% CI: 47.1–133.8) per 100,000 population of ≤15 years and above. The prevalence of TB showed a clear gradient by SEP quartiles. The prevalence of smear positive TB was 5 to 6 times higher in the lower two quartiles of SEP with a prevalence 95.4 (95% CI: 48.0–189.7) and 118.4 (95% CI: 50.9–275.3) compared to highest quartiles of SEP with a prevalence of 19.5 (95% CI: 6.9–55.0) (Table 2). This gradient in prevalence was also present for the levels of education. Persons having no education had a four times higher prevalence of TB (138.6; 95% CI: 78.4–245.0) compared to persons having the highest education (39.3; 95% CI: 9.4–164.9) (Table 2).

Table 2: Prevalence of tuberculosis

| Characteristics          | Number of TB cases detected | Prevalence / 100,000 (95% CI) |
|--------------------------|-----------------------------|-------------------------------|
|                          | Rural                       | Urban                        | All                          |
| Overall prevalence       | 33                          | 86.0 (47.9-154.3)             | 51.1 (27.2-94.1)              | 79.4 (47.1-133.8)             |
| Sex                      |                             |                               |                              |
| Male                     | 24                          | 134.5 (70.8-255.4)            | 70.8 (32.9-152.3)             | 121.7 (69.6-212.8)            |
| Female                   | 9                           | 42.4 (11.4-157.7)             | 31.0 (12.2-78.7)              | 40.3 (13.4-121.4)             |
| Age in years             |                             |                               |                              |
| 15-24                    | 5                           | 47.8 (15.5-146.8)             | 24.1 (5.6-103.1)              | 43.0 (16.2-115.0)             |
| 25-34                    | 3                           | 58.3 (12.0-282.5)             | 0                            | 46.4 (10.0-215.0)             |
| 35-44                    | 6                           | 92.1 (36.3-233.5)             | 41.4 (10.1-170.4)             | 82.0 (36.0-187.2)             |
| 45-54                    | 6                           | 103.0 (33.3-317.8)            | 81.3 (25.1-263.0)             | 99.0 (39.0-254.3)             |
| 55-64                    | 7                           | 212.8 (92.7-488.1)            | 135.6 (31.6-579.6)            | 201.0 (96.3-418.3)            |
| 65+                      | 6                           | 124.5 (30.6-504.8)            | 305.4 (83.4-1112.0)           | 150.0 (53.5-418.3)            |
| Asset quartiles          |                             |                               |                              |
| 1st (Lowest)             | 12                          | 90.6 (41.2-198.9)             | 169.8 (47.7-602.8)            | 95.4 (48.0-189.7)             |
| 2nd                      | 13                          | 122.0 (48.3-307.3)            | 81.8 (27.4-243.8)             | 118.4 (50.9-275.3)            |
| 3rd                      | 5                           | 37.1 (8.9-155.0)              | 35.0 (9.9-123.6)              | 36.6 (11.9-112.5)             |
| 4th (Highest)           | 3                            | 0                             | 24.5 (8.5-70.6)               | 19.5 (6.9-55.0)               |
| Education in Years       |                             |                               |                              |
| 0                        | 15                          | 143.3 (76.7-267.5)            | 99.2 (27.9-352.6)             | 138.6 (78.4-245.0)            |
| 1-5                      | 8                           | 67.4 (25.2-180.3)             | 78.5 (29.2-211.2)             | 69.2 (51.2-153.6)             |
| 6-10                     | 6                           | 61.1 (24.1-154.5)             | 21.1 (5.0-89.2)               | 51.8 (22.6-118.6)             |
| 10+                      | 4                            | 38.0 (4.5-318.1)              | 42.3 (13.0-137.8)             | 39.3 (9.4-164.9)              |
| Occupation               |                             |                               |                              |
| Agri worker              | 4                            | 112.2 (39.1-321.7)            | 0                             | 107.3 (38.4-299.6)            |
| Non-Agri Worker          | 14                           | 191.3 (77.3-472.4)            | 166.3 (79.6-346.8)            | 187.0 (88.3-395.7)            |
| Sales and Service        | 6                            | 104.6 (22.9-477.2)            | 60.8 (23.0-160.6)             | 86.3 (29.7-250.6)             |
| Dependents and others    | (Including housewives)       | 9                             | 46.7 (15.7-139.0)             | 19.4 (6.1-61.2)               | 41.8 (15.7-110.7) |
The prevalence was higher in rural compared to urban settings (86.0 vs. 51.1), and three times higher in males compared to females (121.7 vs. 40.3) per 100,000 adult population. The prevalence increased with age being lowest in persons 15–24 years as 43.0 (95% CI: 16.2–115.0) and highest among 55–64 years as 201.0 (95% CI: 96.3–418.3) age groups. These differences persisted in both the rural and urban stratum. Occupation wise the prevalence was higher in the working class related either with agriculture 107.3 (95% CI: 38.4–299.6) or with non-agriculture works 187.0 (95% CI: 88.3–395.7) compared to the small business or service men 86.3 (95% CI: 29.7–250.6) or of the dependents 41.8 (95% CI: 15.7–110.7), which included a large portion of housewives (Table 2).

The distribution of assets score for the population under survey was 0.38 (95% CI: 0.36–0.38), which was -0.30 (95% CI: -0.30–0.29) for rural and 1.1 (95% CI: 1.03–1.06) for urban areas, indicating the overall lower score by the general population. From the selected 240 TB cases that were routinely identified by the NTP, 137 (57.1%) were from the two uppermost SEP quartiles, with only 5 (2.1%) TB case detected from the lowest SEP quartile. This distribution was markedly different from the distribution of the 33 TB cases identified in the survey, where 25 (75.8%) were from the lower two quartiles, and only 8 (24.2%) from the two upper most quartiles (Table 3).

**Table 3:** SEP distribution of survey population (Households), TB cases from the survey and cases under NTP

| Quartiles   | Survey population | Cases detected in survey | NTP Cases |
|-------------|-------------------|--------------------------|-----------|
| 1 (Lowest)  | 5348 (24.9)       | 12 (36.4)                | 5 (2.1)   |
| 2           | 5364 (25.0)       | 13 (39.4)                | 98 (40.8) |
| 3           | 5348 (24.9)       | 5 (15.2)                 | 108 (45.0)|
| 4 (Highest) | 5367 (25.1)       | 3 (9.1)                  | 29 (12.1) |

Multivariable logistic regression showed that NTP cases were less likely to be classified as having a low SEP compared to survey cases (Odds Ratio [OR] 0.27; 95% CI: 0.11–0.69; p = 0.006) (Table 4). This was also true for urban residence (OR: 0.15; 95% CI: 0.08–0.27; p = 0.001). TB cases older than age 45 years were more likely to be classified as having a low SEP (OR: 2.3; 95%CI: 1.31–4.30 p = 0.004). Sex was not associated with low SEP. There were no interactions (effect modification) between type of TB case and sex, age, or residence.
Table 4: Unadjusted and adjusted OR with CI of the factors associated with detection of TB cases in poor quartiles of population

| Variables          | Quartile | Unadjusted | Adjusted |
|--------------------|----------|------------|----------|
|                    | Upper n  | Lower n    | OR (CI)  | P value  | OR (CI)  | P Value  |
| Sex                |          |            |          |          |          |          |
| Male               | 90       | 86         | 0.79 (0.48-1.31) | 0.378 | 1.08 (0.60-1.90) | 0.773 |
| Female             | 55       | 42         | 0.17 (0.09-0.28) | 0.001 | 0.15 (0.08-0.27) | 0.001 |
| Age                |          |            |          |          |          |          |
| 15-45              | 108      | 71         | 2.30 (1.40-3.90) | 0.000 | 2.30 (1.31-4.30) | 0.004 |
| 45+                | 37       | 57         | 0.24 (0.10-0.55) | 0.001 | 0.27 (0.11-0.69) | 0.006 |
| Residence          |          |            |          |          |          |          |
| Rural              | 46       | 94         | 0.17 (0.09-0.28) | 0.001 | 0.15 (0.08-0.27) | 0.001 |
| Urban              | 99       | 34         | 0.24 (0.10-0.55) | 0.001 | 0.27 (0.11-0.69) | 0.006 |
| Types of TB case   |          |            |          |          |          |          |
| Actively detected  | 8        | 25         | 0.24 (0.10-0.55) | 0.001 | 0.27 (0.11-0.69) | 0.006 |
| (Survey Cases)     |          |            |          |          |          |          |
| Passively detected (NTP cases) | 137 | 103 | 0.24 (0.10-0.55) | 0.001 | 0.27 (0.11-0.69) | 0.006 |

Multiple logistic model includes a. Age (model with “15-45” age group as reference category b. sex (Male as reference) c. residence (rural as reference) and d. Types of TB case (as per mode of detection, actively detected as reference). Quartile has been categorized as lower (1, 2) and upper (3 and 4)

Among cases detected under survey 25 of them belonged to areas where DOTS service is provided by NGO organization like BRAC and Damien Foundation. However only 3 cases were under DOTS, 17 had sought care from other non DOTS sources (9 rural 8 urban) including non licensed providers, pharmacies, other hospitals and graduate private practitioners and half of the cases (50.0%) had no cough at the time of detection (Not shown).

Discussion

Health systems in most instances are inequitable and follow an ‘inverse care law’ providing more to the rich who need them less than to the poor who cannot afford them. Services provided through the government systems are usually claimed to be universal, but practically the greater share of them are received by the upper quintiles of population.37,38 This study focused on the inequalities in accessing free tuberculosis control services (DOTS) in Bangladesh. The findings revealed that nearly 60% of the TB cases detected routinely under DOTS programme belongs to
the upper fraction of the population, on the other hand, 75% of the prevalent cases detected in the survey belongs to lower section of the population.

Notified TB cases in Bangladesh are relatively young and from urban population. These types of patients are less likely to have been classified as having a low SEP. This implies that a large proportion of untreated TB cases remained undetected under routine condition particularly among the poor, particularly in the rural areas. The higher prevalence of TB among the lower quartiles of population also indicates that the poor suffer more and probably delay in detection and treatment.

The availability of Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM) since 2003 enabled augmented advocacy communication and social mobilization (ACSM) and other interventions under NTP to facilitate the currently practiced passive mode of case detection. These activities most likely contributed to the increase in the case notification rate of new smear positive TB cases from 40/100,000 population in 2003 to 74/100,000 population in 2009.\textsuperscript{26} However, potential socio-logical and economical divide of notification was never reported or addressed. Our data indicates that still poor, less educated and worker class people continues to bear the higher prevalence of the disease. The utilization of DOTS services is linked with adequate knowledge of TB and awareness of DOTS programme, which have been reported to be poor in this part of the world.\textsuperscript{12,13,39,40} Targeting the poorer section of population who has less education and less access to media might boost the ongoing ACSM activities.

Achieving wider population coverage of disease-control programmes has been a great health system challenge for the last few decades\textsuperscript{38} globally as well as in Bangladesh. This study provides evidence that in case of TB, coverage of DOT does not guarantee that the services are equitably utilized by all sections of the population. Except for some primary care services like immunization, the poor-rich difference seems to be large in other government provided health services in the country.\textsuperscript{38,41} Even nowadays popular universal health coverage initiatives showed that the initial rapid coverage of up to 75%, reach the rich first, the poor have to wait till the threshold is reached. What the poor get is mostly the result of spilling of or percolation of services.\textsuperscript{38} In case of TB services coverage in Bangladesh, after nearly twenty years of successful DOTS programme implementation, the lack of TB case detection within the subpopulation with lower SEP raises the question of the proper utilization and acceptability of DOTS in this country. Like in other fields of care seeking, evidences from this study again confirmed that mere availability of free diagnostic and treatment services did not guarantee their utilization\textsuperscript{12,31,38}
The issue is probably more complex than coverage and utilization. It is often argued that the relationship between TB and poverty is complex and bidirectional. Mere medical intervention alone will not address this relationship adequately. It is necessary to understand the disease from an epidemiological point of view in relation to its social determinants and consequences. The long duration of TB treatment with its associated conditions of absenteeism from the job, or lack of support in the interim period toll heavily on the poor. Poor cannot cope with the situation easily and ultimately default from treatment, take resort to any other affordable and available short cut like buying drugs over the counter for short period, or use other services. The health system itself very often suffer from rapid turnover of experts, running short of supplies and drugs, or sometimes simply lack of initiative in the absence of committed monitoring and support.

Despite country wide coverage of DOTS services by NGOs like BRAC and Damien Foundation, only 3 cases among the detected cases in the survey were under DOTS at the time of identification. This observation raises the question of system bypass, the role and involvement of the private health sector, delay in detection, and probably other programmatic and behavioral factors in the care seeking pathway. There is anecdotal evidence that people in Bangladesh perceive DOTS centres as only TB treatment centres, resulting in TB suspects (subject with prolonged cough) to bypass DOTS centre and attend either the private sector or non government clinics for their initial consultation and diagnosis. In urban areas of Bangladesh, more than 80% of TB suspects first attended a private sector provider, mostly a non-licensed provider for their initial consultation. Only 16% attended any DOTS centre for their symptoms. The huge TB campaign focusing on “seek TB diagnosis when having cough more than three weeks” should take these issues into consideration.

Indirect evidences of private sector preferences, huge out of pocket health expenses at household level (>60% of total health expenditure), and large system delay in TB diagnosis and management, indicate the inefficient utilization of DOTS in the country. Many TB knowledge attitude and practice (KAP) studies conducted in Bangladesh, India and Pakistan largely support the fact that there are still many barriers for the poor peoples to utilize DOTS. In China, India and other parts of the world studies found that even well implemented DOTS could not reach all sections of population. In fact the financial burden largely weighs heavily on the poorer part of the population and DOTS simply shifts the barriers of expenditures after to before diagnosis.
It seems that the classical five components of DOTS\textsuperscript{46} may not be sufficient to improve the situation. The Stop TB Strategy does acknowledge the need for attention to vulnerable groups, health system strengthening, engagement with the private sector, and community engagement.\textsuperscript{47} However, in addition there is an explicit need for addressing the social determinants of health in relation to TB, to actively reduce barriers for access-to-care, and to provide social support for those in need. These are formidable challenges to be considered but immediate efforts should be taken and directed towards achieving universal and equitable coverage of service throughout the country. How the modulating of social determinants will impact tuberculosis situation is not well documented, but there is indirect evidence that social improvement has a positive effect on health and other development areas. For example microfinance and some other interventions emerged as major strategies to address social conditions like poverty alleviation, women empowerment and overall development in Bangladesh.\textsuperscript{48} Properly instituted and targeted Microfinance could also play a major role in addressing the social determinants of TB as the microfinance philosophy contribute to "double bottom line" of financial and social objectives. Our findings support this fact that TB is associated with both. In a recent systematic review, Boccia et al. concluded that cash transfer and microfinance interventions can positively impact TB risk factors, even though only 1 out of 23 studies targeted TB indirectly, while others were related with social well being and improved health care access.\textsuperscript{49}

The data of this study came from the national prevalence survey which was carried out throughout the country during 2007–09. Therefore, the major strength of the study is that it represents the country population at large by using a valid, albeit not efficient, multi stage cluster methodology. Assets items were directly observed by the trained research assistants and noted in the pretested formats in the field level and a highly motivated supervisory structure was marinated during the whole survey period. Standard operating procedures were followed all the time of data collection. We tried to assess the major pitfalls in using assets as a proxy of wealth and the PCA methodology as an analytical approach.

PCA gives the most reliable results when underlying variables varies across and are well correlated. Extremely distributed variables get either more weight or very low weight producing very high or low standard deviations affecting the results adversely and do not contribute much in differentiating SEP between the groups or households.\textsuperscript{50} As a result, it is advised to exclude those items which are very
common or very rare in the population. We followed this approach by reducing the included assets as much as possible based on the frequency that assets were reported in the population. Alternately, some authors tried including those variables only significant at 1% level based on factor loadings. We decided not to follow this approach, as it is fully data driven.

Combining geographical variation (Rural and urban) in a single asset index may affect the weights estimated for the variables, as some items may be valued differently between urban and rural location. Including assets that are mainly common in urban areas can overestimate the wealth in urban areas and at the same time mask detailed differences in rural areas. We therefore excluded some of the variables like “piped water in the house”, “piped water outside house” and “has motorcycle” from the analysis. In addition, we have adjusted for urban location in the primary analysis assessing SEP and case-detection. In this analysis the rural population has lower score and asset density which shows that the rural population is relatively poorer than the urban population. In the assessment of case detection and SEP, we therefore have included a variable denoting urban/rural population.

Assets with direct health effect were not excluded from our analysis. This is recommended when the analysis has the focus of assessing risk of a health outcome (i.e. TB) by SEP stratum. If not included, the effect of such a variable is “counted twice”, one in the SEP and one in the multivariable analysis. As our focus was to assess case detection method rather than risk of TB, we did not have to resort to further exclusion of variables.

A potential imitation of the study is related to data collection. In some clusters there were difficulties in assessing the assets on the individual households due to dual or composite ownership of certain household assets (e.g. a motorcycle, TV set etc.), multiple household heads with different assets in a same household in some parts of urban areas and hesitancy or hiding some asset items due to different reasons. As such here is room for ascertainment bias. Given the large number of households and the fact that the misclassification is most likely non-differential, we are convinced that the results are a valid representation of the SEP in the general population.

In conclusion it can be stated that the country-wide covered free DOTS programme mostly serves the richer or middle class population and fails to reach the marginalized population where the prevalence of TB is most prominent. Universal and sustainable coverage can never be achieved without reaching the poor. Many
of the TB cases would not have been detected or markedly later if active household search through the survey was not undertaken. Strategies should therefore target the poor and should consider adequate modes of case detection other than the currently practiced passive approach to reach these groups of people from the planning period to the implementation phases of the programme.

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CHAPTER 5

CARE SEEKING IN TUBERCULOSIS: RESULTS FROM A COUNTRYWIDE CLUSTER RANDOMISED SURVEY IN BANGLADESH

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Abstract

Objectives: To explore systematically the care seeking trajectories of tuberculosis (TB) cases up to four subsequent places of care and to assess the type of services provided at each place.

Methods: TB cases detected actively during 2007-2009 national TB prevalence survey and passively under the routine programme in the same period were interviewed by administering a standardized questionnaire. Care seeking and services provided up to four subsequent points were explored. Care seeking was further explored by categorizing the providers into formal, informal and ‘self care’ groups.

Results: A total of 273 TB cases were included in this study, of which 33 (12%) were detected during the survey and 240 (88%) from the TB registers. Out of the 118 passively detected cases who first sought care from an informal provider, 52 (44.1%) remained in the informal sector at second point of care. Similarly, out of the 52, 17 (32.7%) and out of the 17, 5 (29.4%) remained in the informal sector at the third and fourth subsequent points of care, respectively. All the 33 actively detected cases had ‘self care’ at the first point, and 27 (81.8 %) remained with ‘self care’ up to the fourth point of care. Prescribing drugs (59-99%) was the major type of care provided by the formal and informal care providers at each point and was limited to the non-existent practice of investigation or referrals.

Conclusions: Free TB services are still underutilized by TB cases and informal care givers remained the major care providers for such cases in Bangladesh. In order to improve case detection, it is necessary that the National Tuberculosis Programme immediately takes effective initiatives to engage all types of care providers, particularly informal providers who are the first point of care for the majority of the TB suspects.
Introduction

Bangladesh has successfully implemented Directly Observed Treatment, short-course (DOTS), the WHO advocated tuberculosis (TB) control strategy since 1993. Since then, impressive case detection and cure rates were recorded under DOTS. However, from 2006 onwards, case notification became stagnant and even started to show a declining trend.\textsuperscript{1,2} It is likely that a substantial number of cases are not notified under the National Tuberculosis Programme (NTP), and are probably getting treatment from the private sector or not receiving care at all.\textsuperscript{3,5}

The current TB control strategy is based, amongst others, on passive case detection, which is influenced by many health system and patient factors. A patient’s knowledge on TB symptoms, their presence and severity influence on the intention of care seeking.\textsuperscript{6,7} Similarly, availability and access to anti-TB services, and providers’ behaviour also influence care seeking practices and outcomes.\textsuperscript{8,9} Care seeking, therefore is an important determinant that influences not only the individual’s disease status and its prognosis, but also reflects on the epidemiology of TB in a community.

Care givers play a crucial role in the care seeking pathway of individuals with symptoms of tuberculosis. In Bangladesh, health care services are provided by formal and informal providers. Within the organization of TB control in Bangladesh, formal providers are licensed medical practitioners (public or private) who graduated from a medical college, or health workers (public or through Non-governmental Organizations) approved by the NTP, who received training to suspect, examine and refer TB cases to initiate TB treatment at DOTS centres.

Informal providers are non-qualified private practitioners who are not licensed or did not receive any formal training (eg, village doctors, paramedics and pharmacy persons).\textsuperscript{10,11} However, the NTP acknowledges the important role of private sector providers, including informal providers, and urged involve them to achieve TB control objectives through a systematic public-private mix approach.

Informal providers comprise 95% of the total health workers of Bangladesh. They are frequently the point of first care for TB and other chronic conditions due to many conditions including ease of access to their services.\textsuperscript{4,12-15} However, case management within the informal sector remains unpredictable, and outcomes are hardly ever known.\textsuperscript{13,16,17}
With freely available DOTS services throughout the country, it was expected that all persons irrespective of socioeconomic status would access and utilize this service. However, recent findings of the national TB prevalence survey 2007-2009 of Bangladesh revealed that only 9% of actively identified TB cases were known to the NTP, indicating that the others were remaining in the community either without treatment or getting treatment from elsewhere. The same survey showed that care utilisation from DOTS centres was mostly from higher socio economic position (SEP), while prevalent TB cases were mainly seen on the lower SEP strata. SEP was assessed by validated asset items for households and the actively identified cases from survey were compared with passively detected cases under NTP over the identical SEP quartiles. Among the actively detected cases 75.8% were from lower two quartiles, while among the passive TB cases more than half, 57.1%, were from the uppermost two quartiles, 40.8% from the second quartile and 2.1% from the lowest quartile of the population. This distribution did not change after adjustments for other factors or interactions among them. These findings indicate that availability of a service does not ensure its utilisation, as has also been observed in other sectors.

With inadequate, or absence of, initial care of TB cases fueling further transmission of the disease in the general population, it is important to understand the care seeking pathway of the persons with TB symptoms with respect to where care is initiated, and what action is taken by the care provider at the presentation of an individual with chronic cough (as a strong marker for possible TB). The course of the disease is probably much determined at the point of first contact and in the subsequent points.

In this study, we interviewed TB cases detected actively in a national TB prevalence survey, and cases detected passively under routine programme conditions. The objective was to explore their care seeking behavior up to four subsequent points of taking care. The study will identify areas to target by NTP for improved implementation of its activities to increase case finding and appropriate care.

**Methods and materials**

*Setting and Study population*

The study was embedded within the national TB prevalence survey that Bangladesh carried out throughout the country during 2007-2009. This was a cross-sectional survey which included 40 randomly selected clusters. Subdistricts were the...
primary sampling units which were selected proportional to population size. Nearly
52,000 adults (≥ 15 years) were included for sputum examination and 33 new smear
positive TB cases were identified. For this analysis, we interviewed all these 33
actively detected cases and included 6 controls per cluster. The controls were the
most recent passively detected cases under treatment from the TB registers of each of
the 40 clusters’ DOTS centres. All the cases were new smear positive pulmonary TB
cases, and were diagnosed by direct sputum smear microscopy as per NTP
guidelines. The detail of methodology is described elsewhere.18

**Data collection**

Data were collected by interviewing all detected survey cases at their households. A
standard questionnaire was administered by trained survey coordinators
immediately after the diagnosis of a case in the survey. The initial questionnaire was
translated into Bangla, pretested, and revised to incorporate review comments from
users and experts. The survey coordinators received 1 week’s training at the Dhaka
project office. The training included a thorough understanding of the components of
the questionnaire and interview techniques to obtain reliable answers. The
particulars of the 240 NTP cases were obtained from the TB register at the cluster-
specific DOTS centre, after which the persons were visited at their home for an
interview. Informed written consent was taken from all participants. All completed
questionnaires were checked for completeness and appropriateness by a supervisor,
who also reinterviewed a number of cases from randomly selected clusters for cross
checking.

**Measurements**

The interviews provided information on the demographics and symptom profile of
the cases, SEP, care utilisation pattern and services received at each point of care
visited. The demographic data included age, sex, place of residence, levels of
education and occupation. SEP was assessed by asset estimation.19 The symptom
profile recorded the symptoms presented at first care seeking. The care seeking data
provided information on where care was sought, in what order and what measures
were taken by the providers at each point. The detail of socioeconomic data
collection is described elsewhere.5

**Statistical approach**

Data were analyzed using the statistical package Stata 12.0 (Stata Corp., U.S.A.). The
initial general description provides the characteristics of the study population. Age,
education, occupation and symptoms variables were presented in natural subgroups. Asset estimation was based on a set of assets that the household possessed and a weight was allocated to each asset generated through a principal component analysis.\textsuperscript{20} We included items and methods as standardized and followed by the Bangladesh Demographic and Health Survey 2001.\textsuperscript{20,21} The SEP of the study population was divided into quartiles. Care seeking from the first to fourth subsequent points was explored. The types of providers were categorized as formal or informal as described earlier. We added a group as ‘self care’ to denote the use of any treatment obtained outside the formal or informal health sector (eg, home remedies, self medication).

Measures taken at each point of care seeking were grouped in four categories. These were only words of advice offered, investigations ordered and medications given or referred for further investigations. The care seeking and actions taken were reported by the patients at the interview. We did not verify them either by checking prescription or by any other methods. We focused our analysis on the care seeking patterns of those cases who initiated their care seeking trajectory at the informal care sector.

\textbf{Results}

A total of 273 TB cases were included in this study, of which 33 (12\%) were detected during survey and 240 (88.0\%) from the TB registers. Among the participants, 120 (43.9\%) were under 34 years of age, and 176 (64.5\%) were men. Participants were almost equally from rural and urban areas. More than 50\% of the cases presented with more than five symptoms. Most of the participants had cough, including 81.3\% for 15 days or more (Table 1). Among those, the mean delay from onset of symptoms to seek any care from any provider was 31 days, which was 20 days for survey cases and 33 days for the NTP cases under NTP (not shown).
### Table 1: Sociodemographic characteristics of the actively detected survey cases and passively detected NTP cases

| Characteristics          | All N(273) | Survey cases n(33) | NTP cases n(240) | P value |
|--------------------------|------------|--------------------|------------------|---------|
| **Age in years**         |            |                    |                  |         |
| 15-34                    | 120        | 8                  | 112              | 0.028   |
| 35-54                    | 87         | 12                 | 75               |         |
| 55+                      | 66         | 13                 | 53               |         |
| **Sex**                  |            |                    |                  |         |
| Male                     | 176        | 24                 | 152              | 0.290   |
| Female                   | 97         | 9                  | 88               |         |
| **Residence**            |            |                    |                  |         |
| Rural                    | 140        | 20                 | 120              | 0.253   |
| Urban                    | 133        | 13                 | 120              |         |
| **Education**            |            |                    |                  |         |
| 0                        | 71         | 15                 | 55               | 0.039   |
| 1-5                      | 71         | 8                  | 65               |         |
| 6-10                     | 68         | 6                  | 62               |         |
| 10+                      | 63         | 4                  | 58               |         |
| **Occupation**           |            |                    |                  |         |
| Agriculture based        | 37         | 4                  | 33               | 0.003   |
| Daily wagers             | 89         | 14                 | 75               |         |
| Sales and services       | 115        | 6                  | 109              |         |
| Others                   | 32         | 9                  | 23               |         |
| **Asset Quartiles**      |            |                    |                  |         |
| 1st (Lowest)             | 17         | 12                 | 5                | 0.000   |
| 2nd                      | 111        | 13                 | 98               |         |
| 3rd                      | 113        | 5                  | 108              |         |
| 4th                      | 32         | 3                  | 29               |         |
| **Presence of cough**    |            |                    |                  |         |
| Yes                      | 226        | 29                 | 197              | 0.408   |
| No                       | 47         | 4                  | 43               |         |
| **Duration of cough**    |            |                    |                  |         |
| Less than 14 days        | 51         | 6                  | 45               | 0.937   |
| ≥ 15 days                | 222        | 27                 | 195              |         |
| **Number of symptoms**   |            |                    |                  |         |
| ≤ 2                      | 44         | 4                  | 40               | 0.556   |
| 3-4                      | 79         | 8                  | 71               |         |
| 5+                       | 150        | 21                 | 129              |         |

Care seeking in tuberculosis
Among the 240 cases detected passively under NTP, 118 (49.1%) sought initial care from informal providers, 106 (44.2%) from formal providers, and 16 (6.7%) used self-care. All of the 33 actively detected cases had initial ‘self care’ and together with the 16 passively detected cases, the proportion of ‘self care’ at the first point of care was 49 (17.9%) among all cases (Figure 1). Out of the 118 passively detected NTP cases with initial care from the informal sector, 52 (44.1%) remained in the informal sector, while 61 (51.7%) switched to a formal provider for care at the second point of care. Again, among the 52 who remained in the informal care sector, at the third point of care 32 (61.5%) migrated to the formal care sector, while 17 (32.7%) remained in the informal sector. The proportion of patients who remained in the informal care sector up to the fourth point care was five (29.4%) of those starting their health seeking behavior in the informal sector (Figure 1). Among the 16 (6.7%) NTP cases who reported self-care as their initial strategy, ultimately four (25.0%) remained in this stage up to the fourth point of care, three (18.8 %) moved to the informal sector and nine (56.2%) subsequently migrated to the formal care sector. Among the active detected cases, all of whom had self-care as the initial strategy, 27 (81.8%) remained at this stage before being detected by the survey. Among the remaining six, three shifted to the formal sector at the second point of care, while the other three switched between informal and formal providers in the subsequent points of care (Not shown).

Fig. 1: Care seeking at different points of care
We looked into measures taken at each point of care by the formal and informal providers. In the formal care sector, the primary action was to prescribe drugs at each point of care starting with 79 (74.5%) at the first point, 43 (70.5%) at the second point, 19 (59.4%) at the third point and 10 (91%) at the fourth point of care. Ordering diagnostic investigations varied from 19 (17.9%) at the first point of care, to 14 (22.9%) at the second, 10 (31.2%) at the third, and 1 (9%) at the fourth point of care. Referral for further investigation was seldom done (0-2%). The informal providers, on the other hand, prescribed drugs in 80-99% of the encounters, and seldom ordered diagnostic investigations or referred the individual for further investigations at any of the four points of care (Figure 2).

![Fig. 2: Actions taken if care sought from formal and informal providers](image)

The reasons for not seeking care at all were available only from the 33 survey cases. The major reasons were not considering symptoms serious enough, and monetary constraints.

**Discussion**

Our study showed that most of the initial care seeking by passively identified TB cases happened at the informal sector or was limited to self-care. At each following round of care seeking a third to a half remained in the informal care sector. Among
the actively detected cases, more than 80% remained in the self-care sector up to the time of their identification by the survey. Case management in the informal sector was restricted to prescribing any medications, with non-existence of any diagnostic investigations or referrals.

Preference for informal providers as an initial place of care has been reported from Bangladesh and elsewhere.\textsuperscript{3-5,9,12} In chronic conditions where symptom onset is slow and insidious like tuberculosis, people usually consult with an informal provider available at hand or consume over the counter drugs. This behavior can cause a marked delay in starting appropriate TB medication, given the fact that TB medication in line with the NP guideline is seldom present in the informal health sector. This has been observed in earlier studies from Bangladesh.\textsuperscript{4} Our study adds the important finding that this preference of the informal sector persists throughout the care seeking trajectory. The lack of (referral for) diagnostic investigation can cause additional systems delay (between care seeking and starting appropriate treatment). An earlier study reported that this type of delay could be more than 10 weeks.\textsuperscript{4} Delay to reach appropriate care and treatment impacts on the course of the disease and may result in unfavorable outcomes and ongoing transmission.\textsuperscript{22} From a programmatic point of view, this situation leads to a marked under reporting of TB cases.

Care seeking from the informal sector is not limited to TB only, but is rather a common feature for all chronic conditions in Bangladesh.\textsuperscript{15,23} It is suggested that the presence of huge numbers of informal providers in rural and urban areas, their easy accessibility due to reduced cost and minimal levels of stigma when attending such providers encourage people to seek care from this sector first.\textsuperscript{15,23,24} A good portion of them are simple drug sellers providing drugs without further diagnostic procedures.\textsuperscript{12} This easy access to informal providers stimulates “shopping for care”, when care is sought from informal providers subsequently one after one, as observed in our study. In Malawi, care seeking among patients with TB noted that multiple contacts in the range of 1-15 were made before the diagnosis.\textsuperscript{25} Similarly, in Vietnam, patients made on average 1.3 contacts and 2.5 visits per provider before getting appropriate TB services, even though the size private sector was very small.\textsuperscript{26}

We observed that the case management was not altogether different in the formal and informal sector with respect to prescribing drugs. However, unlike in the formal sector, there was almost a complete absence of diagnostic procedures and referrals in the informal sector. We need to carefully interpret these findings as we
do not have information on what drugs were prescribed by the providers. Retrospective recording of actual drugs through patient interviews is difficult and in most cases unreliable. In Bangladesh, fixed dose combination (FDC) anti-TB drugs are almost exclusively available at DOTS centres. This implies that medication provided through the informal sector is unlikely to be adequate for the management of TB. However, formal providers can manage TB cases outside the context of DOTS centers. As such, mismanagement of TB can also occur in the formal sector, given the low occurrence of diagnostic investigations.

A study in Malawi provided insight into the type of medication provided to individuals with TB symptoms but without a formal diagnosis. The authors reported that 61% of cases had been treated with antibiotics like co-trimoxazole, doxycycline, and penicillin.25

NTP also recognizes the absence of standard practices in the private sector and the lack of sufficient interaction and formal linkages between NTP and these private sector providers. The lessons learnt from studies aimed at establishing connections between formal and informal healthcare providers remain unexplored.13,27 Our study indicates that despite the country coverage by DOTS, and public-private-partnership activities undertaken by the NTP, the impact did not result in reducing the disconnect between NTP and the informal health sector. In a recent attempt to improve the situation, NTP in partnership with icddr,b and US Agency for International Development (USAID) is implementing a “Translating research into action (TRAction)” project to test different implementation strategies, with a clear role for the informal providers. This current study suggests that an attempt is timely and needed.

One of the potential limitations of the study is the potential for minor selection bias. Although all participants were randomly selected, the selection of clusters was not stratified by urban/rural setting. The study sample therefore does not fully represent 70% of the rural population in Bangladesh. There was also a slight over-representation of men. However, the national case notification is more or less static at 3:1 male to female since the inception of DOTS in 1993.1 The strengths of the study are that the cases were interviewed at home by trained research coordinators providing an enabling study setting. We explored the care seeking of actively and passively detected cases which would cover care seeking from a wider perspective of two different kinds of cases, one who is probably in the early phase of the disease process and the other probably in a more advanced condition. Moreover, we have
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covered the care seeking up to the fourth point of care, which is expected to give a more comprehensive picture of the care seeking by the TB cases in Bangladesh.

In conclusion, it can be said that most of the initial care seeking by different types of TB cases was sought from informal providers or was limited to self-care, and that a large proportion of these cases remained in the informal sector during subsequent care seeking. It is imperative that the NTP should immediately take the initiative to engage all types of care providers, particularly the informal providers. It is also necessary to strengthen the ongoing advocacy communication and social mobilization activities to increase awareness on key TB symptoms, availability of diagnosis and free treatment in an attempt to stimulate appropriate care seeking, and to prevent unnecessary delay in TB case management.

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CHAPTER 6

FACTORS ASSOCIATED WITH POOR KNOWLEDGE AMONG ADULTS ON TUBERCULOSIS IN BANGLADESH: RESULTS FROM A NATIONWIDE SURVEY

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Abstract

Introduction: In 2012, Bangladesh continues to be one of the top 10 highest tuberculosis (TB) burden countries in the world. Although free diagnosis and management for TB is available throughout the country, case notification rate for new smear positive (NSP) cases under the national TB control programme (NTP) remained at around 70/100,000 population and have not changed much since 2006. Knowledge on TB disease, treatment and its management could be an important predictor for utilization of TB services and influence case detection under the NTP. Our objective is to describe knowledge of TB among newly diagnosed TB cases and community controls to assess factors associated with poor knowledge in order to identify programmatic implications for control measures.

Methods: Embedded in TB prevalence survey 2007-2009, we included 240 TB cases from the TB registers and 240 persons ≥ 15 years of age randomly selected from the households where the survey was implemented. All participants were interviewed using a structured, pre-tested questionnaire to evaluate their TB knowledge. Regression analyses were done to assess associations with poor knowledge of TB.

Results: Our survey documented that overall there was fair knowledge in all domains investigated. However, based on the number of correct answers to the questionnaires, community controls showed significantly poorer knowledge than the TB cases in the domains of TB transmission (80% vs. 88%), mode of transmission (67% vs. 82%), knowing ≥ 1 suggestive symptoms including cough (78% vs. 89%), curability of TB (90% vs. 98%) and availability of free treatment (75% vs. 95%). Community controls were more likely to have poor knowledge of TB issues compared to the TB cases even after controlling for other factors such as education and occupation in a multivariate model (OR 3.46, 95% CI: 2.00-6.09).

Conclusions: Knowledge on various aspects of TB and TB services varies significantly between TB cases and community controls in Bangladesh. The overall higher levels of knowledge in TB cases could identify them as peer educators in ongoing communication approaches to improve care seeking behavior of the TB suspects in the community and hence case detection.

Key words: Tuberculosis; Knowledge; Community; Bangladesh
Introduction

Bangladesh started the implementation of Directly Observed Treatment, Short Course (DOTS), the World Health Organization’s (WHO) advocated strategy for tuberculosis (TB) control, in 1993. Under the DOTS strategy, diagnosis and treatment of TB was made available free of cost from over 1000 centres throughout the country. However, at the end of 2012, after 20 years of DOTS implementation, Bangladesh remained one of the 22 high TB burden countries in the world, with an estimated prevalence of new smear positive (NSP) TB cases among adults above ≥ 15 years as 79.4/100,000.\textsuperscript{1-3} The case notification rate for NSP TB in Bangladesh is estimated to be low and remained static from 2006 onwards at around 70/100,000 per year.\textsuperscript{2} It has also been observed that in over 50% of cases care seeking for TB-related symptoms starts in the informal sector and often remains outside of the National TB control Programme (NTP) for several health care visits, potentially leading to treatment delay and ongoing transmission.\textsuperscript{4}

DOTS is a therapeutic based approach which largely depends on the willingness of the affected person to accept and adhere to it. This is particularly true in Bangladesh, where case detection under the NTP is passive. Care seeking decisions are often based on knowledge of a disease, availability of services and the perceived quality of care. Knowledge therefore could be an important predictor of not only of initial care seeking behavior but also indirectly of the course of the disease and its outcomes.\textsuperscript{5-8}

Considering the importance of people’s knowledge of the availability and effectiveness of the DOTS programme, the NTP and its partners have been engaged in Advocacy Communication and Social Mobilization (ACSM) campaigns, largely funded by The Global Fund to fight AIDS, TB and Malaria (GFTAM). These campaigns should raise the general population’s awareness of the importance of TB, the need for early diagnosis, and the availability of free TB treatment at DOTS facilities. The impact of these ACSM campaigns has never been fully measured. A recent TB-monitoring report for the country identified considerable shortcomings in the organization of ACSM activities that question their potential efficacy.\textsuperscript{9} These shortcomings include inadequate human resources to carry out the activities, inadequate attention to urban settings, and failure to lay out a clear plan to address stigma, discrimination and gender issues.\textsuperscript{9}

There is no direct evidence on how well ACSM campaigns can convey information, but anecdotal evidence suggests that the information provided may not reach the intended population in a meaningful way.\textsuperscript{10} We therefore added a sub-study to the
latest national TB prevalence survey, which was carried out in 2007-2009. Our objective was to assess knowledge of TB symptoms, routes of transmission, and treatment options. Furthermore we explored factors associated with poor knowledge. Apart from assessing the overall level of knowledge of TB in the country, we assessed whether recently diagnosed TB cases differed in their knowledge compared to the community controls, and could therefore potentially serve as “peer educators”. It is expected that information from this study might have implications for future planning of TB-control measures in Bangladesh.

Materials and methods

Setting and sampling: This study was a part of the national TB prevalence survey which was carried out in 2007-2009. This was a population based cross-sectional survey, which randomly included 40 clusters, equally from urban and rural areas, using a proportion to population size sampling strategy. The unions or sub-districts in rural areas and wards or zones in urban areas were primary sampling units (PSU). From each unit, one mauza or miullah (lowest level administrative unit) was selected as a study cluster. Households were selected in each cluster from a random starting point with consecutive inclusion until the estimated numbers (1400 per cluster was targeted to attain the sample size) of individuals were listed. A total of 52,000 individuals (≥ 15 years of age) were included in the national survey.

For this study, we included the six most recently registered pulmonary TB (PTB) cases from the local DOTS centre and six adults randomly selected from the survey’s sampling frame as a comparison group from each cluster. This provided a sample of 240 TB cases and 240 adults from the general community population. All included cases were new smear positive (NSP) pulmonary TB cases, passively diagnosed through the ongoing NTP programme. All cases were on treatment at time of inclusion in the study. Community controls were contemporary to the selected TB cases from each cluster. No refusal was reported in this survey. When an individual was absent a second attempt was made to reach her/him. Only one individual per household was included.

Data Collection: Information on TB knowledge was obtained through face-to-face interviews with the participants by trained interviewers. The interviewers were trained one week at Dhaka and further one week at field level in a pilot cluster. A structured questionnaire was prepared based on NTP monitoring guidelines, and other knowledge studies. The questionnaire included socio-demographic and TB
knowledge items. The questionnaire was translated into Bangla and pretested for its clarity and understandability before finalization. Pretesting of the questionnaire was done in Dhaka and in a cluster area not included in the sample. Pre testing was performed by the supervisors and the results were discussed among the research team for necessary modification before finalization. There were two field level supervisors and one lab supervisor in each of the team engaged in the survey. The supervisors were qualified researchers with at least 10 years of field level experiences in conducting surveys. All questionnaires were checked by the supervisor for accuracy and completeness. The supervisor also re-interviewed 5% of all cases to cross check the accuracy of information. Every alternate cluster was included for cross checking equally from rural and urban areas. No major discrepancies were reported.

Measurements: The interview collected information on demographic parameters including age, sex, and area of residence, levels of education, and occupation status. The questions on TB knowledge included the domains of symptoms, transmission and treatment.

Statistical approach: Data were checked, processed and analyzed by using the Statistical package STATA 12.0 (Stata Corp. TX. U.S.A.). Residence was dichotomized in urban and rural setting. Age and occupation were categorized into three groups, and education into four based on obtained frequencies. Under occupation the category ‘manual labour’ included all types of workers (agriculture workers, day labourer, rickshaw pullers etc.), ‘sales and services’ included shop keepers, public and private sector service holders etc., and ‘dependants’ included housewives, students, vagabonds, beggars etc.). All TB-knowledge questions were categorized into correct or incorrect according to NTP guidelines (11). We compared the proportions of participants providing correct answers for each knowledge item among TB cases and community controls. We generated a ‘knowledge score’ as the composite score of five key questions (1 for correct, 0 for incorrect answer) resulting in a range of 0 to 5. The key questions explored the common communication messages of the national and global TB programme ACSM activities, which included that (i) TB is contagious, (ii) TB is transmitted by airborne spread, (iii) cough is a main symptom of TB, (iv) TB is curable and (v) TB treatment is available free at DOTS centre. The NTP has used these messages for about two decades based on their high sensitivity (chronic cough as a symptom of TB) and specific programme related information. From these messages we derived the five questions and developed the variable “TB-knowledge” assigning ‘poor’ to those who answered
univariable regression analyses assessed the association between the demographic variables and “poor TB-knowledge”. In the multivariable analyses, the association of interest was between TB-knowledge and type of participant (TB cases vs community control). We included only those dependent variables that changed the odds ratio of the initial association by more than 10%. We assumed that TB-knowledge is directly linked with levels of education, and tested for effect modification between each of the variables and education, by means of the log-likelihood ratio test.

Ethical consideration: Ethical clearance was obtained from the institutional review board (IRB, FWA-00001468) of the International Centre for Diarrhoeal Diseases Research, Bangladesh (icddr,b). Written consent was obtained from all participants.

**Results**

Approximately half of the study population was between 15-34 years of age in both groups with significantly more males among TB cases (63%) than community controls. There were also significant differences between the TB cases and community controls in their distribution of education, occupation and smoking status (Table 1).

TB cases in comparison to community controls provided significantly more correct answers for most TB-knowledge questions (Table 2). That TB is a contagious disease was correctly identified by 88.8% and 80.4%, and TB transmission modes by 82.5% and 67.1%, of the TB cases and community controls respectively. There was no difference between the two groups in identifying cough as a TB symptom. However, other TB-related symptoms were more often correctly identified by TB cases compared to community controls. Correct answers to the questions related to programmatic aspects of TB management were high in both groups, but significantly higher among TB cases. As a result, TB cases had a higher overall ‘TB-knowledge score’ than community controls (Table 2).
Table 1: Socio demographic characteristics of the participants

| Characteristics          | TB cases 240, n(%) | Community control 240, n(%) | P value* |
|--------------------------|--------------------|-----------------------------|----------|
| Age groups (Years)       |                    |                             |          |
| 15-34                    | 112 (46.7)         | 127 (52.9)                  | 0.150    |
| 35-54                    | 75 (31.3)          | 76 (31.7)                   |          |
| ≥ 55                     | 53 (22.0)          | 37 (15.4)                   |          |
| Sex                      |                    |                             |          |
| Male                     | 152 (63.3)         | 116 (48.3)                  | 0.001    |
| Female                   | 88 (36.7)          | 124 (51.7)                  |          |
| Residence                |                    |                             |          |
| Rural                    | 120 (50.0)         | 120 (50.0)                  | 1.000    |
| Urban                    | 120 (50.0)         | 120 (50.0)                  |          |
| Education                |                    |                             |          |
| 0                        | 101 (42.1)         | 78 (32.5)                   | 0.001    |
| 1-5                      | 65 (27.1)          | 47 (19.6)                   |          |
| 6-10                     | 62 (25.8)          | 85 (35.4)                   |          |
| 10+                      | 12 (5.0)           | 30 (12.5)                   |          |
| Occupation               |                    |                             |          |
| Sales & services         | 109 (45.4)         | 33 (13.8)                   | 0.001    |
| Manual labour            | 108 (53.7)         | 93 (38.7)                   |          |
| Dependents               | 23 (9.6)           | 114 (47.5)                  |          |
| Smoker                   |                    |                             |          |
| Yes                      | 128 (64.0)         | 72 (36.0)                   | 0.001    |
| No                       | 112 (40.0)         | 168 (60.0)                  |          |

*p < 0.05, Chi X² values
Table 2: Knowledge about TB among adult TB cases and community controls

| Knowledge items                                      | Includes correct Answer | Community control n (%) | p-value* |
|------------------------------------------------------|-------------------------|-------------------------|----------|
|                                                      | TB cases n (%)          |                         |          |
| TB Transmission                                      |                         |                         |          |
| TB contagious / Infectious                           | 213 (88.8)              | 193 (80.4)              | 0.011    |
| TB transmits by air (Cough/sneeze)                  | 198 (82.5)              | 161 (67.1)              | 0.001    |
| Symptoms of PTB                                      |                         |                         |          |
| Know ≥ 1 suggestive symptoms including cough         | 210 (87.5)              | 188 (78.3)              | 0.001    |
| Cough                                                | 215 (89.5)              | 207 (86.5)              | 0.263    |
| Fever                                                | 188 (78.3)              | 144 (60.0)              | 0.000    |
| Chest pain                                           | 158 (65.8)              | 131 (54.6)              | 0.012    |
| Loss of weight                                       | 187 (77.9)              | 127 (52.9)              | 0.001    |
| Blood in cough                                       | 204 (85.0)              | 114 (47.0)              | 0.001    |
| Difficult breathing                                  | 153 (63.8)              | 127 (52.9)              | 0.016    |
| Night sweating                                       | 112 (46.7)              | 51 (21.5)               | 0.001    |
| Loss of appetite                                     | 178 (74.2)              | 111 (46.2)              | 0.001    |
| TB treatment, programmatic information               |                         |                         |          |
| TB curable                                           | 237 (98.8)              | 216 (90.0)              | 0.001    |
| TB treatment free                                    | 229 (95.4)              | 180 (75.0)              | 0.001    |
| Knowledge score (Median IQR)*                        | 5 (4-5)                 | 4 (3-5)                 | 0.001    |

*p < 0.05 Chi X²-values, ? Ranksum test

Table 3 shows the results of the regression analyses. The univariable logistic regression showed significantly more often “poor knowledge” in community controls compared to TB-cases (OR: 3.12, 95% CI: 1.96-4.97; p=0.001). The odds of “poor knowledge” was higher in women compared to men (OR: 2.04, 95%CI 1.32-3.16), urban compared to rural residents (OR: 1.75, 95%CI: 1.12-2.71), and “dependents” compared to other occupational groups (OR: 2.22, 95%CI: 1.28-3.84). Having had formal education was associated with a lower odds of “poor knowledge” (Table 3).
Table 3: Factors related to poor knowledge on TB

| Factors                | TB Knowledge | Univariable | Multivariable |
|------------------------|--------------|-------------|--------------|
|                        | Poor* n (%)  | OR (95% CI) | p-value      |
|                        |              | OR (95% CI) | p-value      |
| Case status            |              |             |              |
| TB case                | 31 (12.9)    | 1           | 1            |
| Community control      | 76 (31.7)    | 3.12 (1.96-4.97) | 0.001     | 3.46 (2.00-6.09) | 0.001 |
| Sex                    |              |             |              |
| Male                   | 45 (16.8)    | 1           | 1            |
| Female                 | 62 (29.2)    | 2.04 (1.32-3.16) | 0.001     |
| Age groups in years    |              |             |              |
| 15-34                  | 59 (24.7)    | 1           | 1            |
| 35-54                  | 27 (17.9)    | 0.66 (0.39-1.10) | 0.116     |
| ≥ 55                   | 21 (23.3)    | 0.92 (0.52-1.64) | 0.799     |
| Education in Years     |              |             |              |
| None                   | 53 (29.6)    | 1           | 1            |
| 1 - 5                  | 17 (15.8)    | 0.43 (0.23-0.78) | 0.026     | 0.43 (0.23-0.81) | 0.008 |
| 6 or more              | 37 (19.6)    | 0.59 (0.36-0.94) | 0.006     | 0.47 (0.27-0.80) | 0.006 |
| Residence              |              |             |              |
| Rural                  | 42 (17.5)    | 1           | 1            |
| Urban                  | 65 (27.1)    | 1.75 (1.12-2.71) |          |
| Occupation             |              |             |              |
| Sales & Services       | 27 (19.0)    | 1           | 1            |
| Manual labour          | 33 (16.4)    | 0.83 (0.47-1.46) | 0.533     | 0.60 (0.33-1.09) | 0.092 |
| Dependents             | 47 (34.3)    | 2.22 (1.28-3.84) | 0.004     | 0.95 (0.49-1.84) | 0.873 |

Note: From a multiple logistic model including a) case status, TB cases as reference category, b) education modeled as dummy variables with the category ‘0 or no education’ as reference group, c) agegroup modeled as dummy variables with category 15-34 years as reference group, d) sex, male as reference group, e) residence, rural as reference group f) occupation modeled as dummy variables with the category ‘sales & service’ as reference group.

Among the demographic variable examined, only education and occupation changed the odds ratio between TB cases or community controls and TB-knowledge, and were therefore included in the multivariable model as potential confounders. In this model, community controls were still significantly more likely to have poor knowledge compared to TB cases (OR 3.46, 95% CI: 2.00-6.09) (Table 3). We did not find any significant effect modification by education (Not shown).
Discussion

The present study reported an overall fair level of knowledge of cough as an important symptom of TB, ways of transmission, curability and availability of free treatment in Bangladesh. Despite this, knowledge of community controls of TB symptoms other than cough and the availability of free treatment was markedly lower than that of TB cases. Overall, community controls had more than 3 times higher odds of having “poor knowledge” compared to TB cases.

An urban study among TB patients at exit from DOTS centres in Bangladesh also reported knowledge of TB symptoms. Only 61% of the participants recognized “cough more than 3 weeks” as an important symptom of TB and only 56% knew that TB could be transmitted through “sneezing and coughing”. More than 90% of the respondents reported that TB could be cured and Specific drugs are given through DOTS centre. On the other hand, data from 2007 Demographic Health Survey (DHS) from country wide sample of ever married women (~11,000) showed an adequate level of knowledge that TB is curable (78%), but poor knowledge on transmission (7%). Knowledge of TB symptoms, transmission and curability was studied in neighbouring and other countries and was reported variedly. A study from India, from a country wide sample reported correct knowledge on TB transmission in 55.5%, and curability in 83.5% of respondents. In Vietnam newly diagnosed TB cases had high knowledge on transmissibility (87.1% - 89.3%), airborne infection (65.7% - 78%), cough as a symptom (92% - 93%), curability (69.6% - 80.2%) and free availability of treatment (45%-57.0%) (20). In facility based studies from India and Tanzania poor knowledge among TB patients was reported on cause of TB and mode of transmission. Interestingly, Luis et al. from Angola, reported lower knowledge on key TB symptoms (12.9%), curability (61.0%), where to treat (30.4%), but higher intent to seek diagnosis and treatment, among those who had heard about TB (OR 3.1 (1.4-6.8, p=.005) among community people, highlighting the importance that people impart on diagnosis and treatment despite poor basic knowledge on TB. None of the studies linked knowledge in the general population directly to ACSM activities, making the value of these activities difficult to judge.

The significant association of community controls who had never had TB with “poor knowledge” in comparison to TB cases in this study was probably due to the recent exposure of TB cases to information during their diagnosis and treatment under DOTS, which usually includes a counseling session. The significant association of persons without education with poor TB-knowledge implies that information about
TB may not be reaching this group in an effective manner. We do not know of ACSM activities in the field of TB in Bangladesh that clearly differentiated their mode of delivery for information for specific groups such as those without formal schooling. Tasnim et al. reported the main source of information was from television (46.8%), followed by physicians (18.2%) and family members or friends (14.6%). The role of print media (3.3%) and non-governmental organization (NGO) workers (7.9%) was less than other sources. However, the scenario could be different in rural areas in terms of context, language and modes of delivery of messages and all of these should be considered. The efficacy of modes of information delivery was explored in a recent study in Pakistan. The researchers found that awareness of TB was higher among urban dwellers and literate people among those who were exposed to mixed such as both media and community members. The study also found that people from different backgrounds might have different preferences for source of information.

The association of “poor knowledge” with urban residency may be related to the larger presence of NGOs in rural compared to urban areas in Bangladesh. The NTP DOTS programme also started at least 10 years later in the urban setting compared to the rural setting. The relatively worse conditions in urban areas of Bangladesh is also seen in other important public health issues, like low immunization coverage among urban slum children and the high proportion of malnutrition among this population group. Dissemination of information by individuals with TB in closely knit communities in the rural areas may have also contributed to the higher level of TB-knowledge in those communities.

In our study, women were more likely than men have poor TB-knowledge (Table 3). Perhaps, this could explain the persistent lower case detection in women compared to men in Bangladesh. However, it remains unclear if higher levels of TB-knowledge themselves actually lead to improved care seeking behaviour, diagnosis and treatment. A recent systematic review identified gender-specific differences in TB stigma including financial and social barriers that may account for lower case detection rates among women compared to men.

Although NTP of Bangladesh has put a strong emphasis on ACSM activities, up to now there has been no formal evaluation of the impact of these activities. The current study provides some indirect evidence that ACSM activities might have an effect in increasing awareness of TB in the general population. Key elements of TB like the importance of cough, the transmissibility and operational characteristics were
known by the majority of people. Areas where TB knowledge can be improved were also identified, including additional symptoms other than cough, and operational issues like the availability of free treatment.

Our study suggests that TB cases could be a useful source to provide this information. Not only is their knowledge of disease adequate, they will have a personal experience and may be better able to address societal aspects of the disease specific to their communities. A patient friendly atmosphere is important for the NTP to provide services that women and illiterate or poor individuals will not shy away from. Peers educators can play an important role in this regard and have been shown to be an effective intervention in HIV-prevention strategies among the youth. In India, Van Rompay et al. described a peer-led programme aimed at increasing HIV-awareness in rural communities with high rates of illiteracy. Educators were women’s self-help group leaders and barbers. The authors concluded that the programme was an effective way of disseminating culturally appropriate health-related messages.

In the field of TB, peer educators have been used in preventive strategies in universities, and hard-to-reach populations like the homeless and injecting drug users. Such strategies resulted in higher levels of understanding of the disease, and the need for early diagnosis and treatment. Particularly, in settings where most health care seeking starts in the informal sector. Although it is unlikely that the level of knowledge is the sole driver of care seeking behaviour for TB, addressing knowledge gaps in the population could prove beneficial for TB-control in general. The role of a DOTS club comprising TB patients, local support groups, local religious group or work place peers could be explored. Similar experiences reported from, Chili, Peru, Ethiopia and Vietnam demonstrated that peer support groups like a TB club led to significant improvements in access, utilization and outcomes.

Our study provides insight into levels of TB-knowledge of the general population in Bangladesh. However we need more information on care seeking behaviours. A recent nation-wide study in Bangladesh examined care seeking behaviour among TB cases. Over 50% of the cases started care seeking with informal providers not related to the NTP. Moreover, nearly half of them remained in the informal sector at multiple subsequent points of care seeking. The main reason delays in seeking care was the perception that symptoms were not serious enough. The role of the severity of disease in care seeking was also previously reported by Karim et al. in
a large qualitative study in Bangladesh.\textsuperscript{24} They emphasized the involvement of TB cases in interactive communication and education activities to convey the importance of early care seeking for TB-related symptoms.\textsuperscript{24}

Our study represents a nationwide sample of TB patients and community controls and hence provides representative information on TB knowledge. The main limitation of the study is that it was conducted in those sites where the prevalence survey was carried out, potentially “sensitizing” the study population for TB. If anything, this effect would be expected to have reduced the differences between the TB cases and community controls.

The study provides useful information on TB knowledge among the community people and TB cases. This information could be helpful for ongoing ACSM activities to rethink and reorganize its strategies and targets. With the availability and abundance of mobile phones and other digital media, innovative and more individualized approaches can also be tried to reach those populations in need. For example, NTP or its partners could explore the effect of cross media synergy on access to TB information by different sects of people and its ultimate impact on case detection, reducing delays and enhancing treatment adherence. It is also important to explore the possible role of treated TB patients as peer educators in these activities.

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Chapter 6

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CHAPTER 7

COMPARISON OF MACROSCOPIC AND MICROSCOPIC ASSESSMENT OF SPECIMENS COLLECTED FOR THE DIAGNOSIS OF TUBERCULOSIS

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Abstract

Diagnosis of tuberculosis in a field setting depends on the quality of specimens submitted for smear-microscopy. Macroscopic assessment (sputum or saliva) of the specimen for suitability for further examination is common practice in routine care. We examined whether macroscopic assessment could correctly identify sputum specimens based on four published algorithms using microscopic features in the setting of active case finding in a community survey.

The study included 901 randomly selected adults who reported cough for 3 weeks or more in the national tuberculosis prevalence survey in Bangladesh. A single specimen of each was assessed with microscopy and microscopy (Gram-stain) to classify it as either sputum or saliva. The primary outcome was the agreement between the two assessment methods (Kappa statistic).

From 901 specimens, 561 (62%) were macroscopically classified as saliva and 340 (38%) as sputum. From these, 888 Gram-stained slides could be examined for microscopic features. The agreement between the macroscopic assessment with any of the four microscopy algorithms for sputum was very poor (all Kappa’s below 0.1).

While macroscopic assessment of submitted specimens might be of value in routine care, it is not warranted in a setting of active case finding in a community survey. Submitting a specimen in the first place should be the primary goal in this setting.

Keywords: Macroscopy, microscopy, sputum quality, survey, tuberculosis
Introduction

Tuberculosis (TB) is a disease of global importance. One-third of the world's population is estimated to have been infected with Mycobacterium tuberculosis and eight million new cases of tuberculosis arise each year.\(^1\) TB diagnosis can only be made reliably by demonstrating the presence of tubercle bacilli in the sputum by means of microscopy and/or culture in the laboratory. The gold standard for diagnosing pulmonary tuberculosis is culture of a sputum specimen. However, due to lack of access to culture facilities and the long turn-around times involved with sputum culture, the cornerstone of the diagnosis of tuberculosis is still the microscopic examination of sputum specimens for acid-fast bacilli (AFB) in many developing countries including Bangladesh.

Under this condition it is very important that a high quality sputum specimen is available for microscopic examination in order to diagnose TB accurately. Patients frequently provide pure saliva or very small amounts of sputum in saliva instead of an appropriate, purulent, sputum specimen. Saliva smears are in general more likely to be negative or have an AFB density below the threshold of microscopy detection than sputum smears.\(^2\) A negative result issued on examination of such a specimen is misleading, since it implies that a correct sputum specimen has been examined. This holds particularly true in settings where AFB microscopy is used in the context of large-scale TB prevalence surveys, where participants are less likely to be able to produce an adequate specimen.

These surveys are currently being prepared or implemented in a large number in countries in an attempt to provide data for the assessment of the progress on goal 6 of the Millennium Development Goals.\(^3\)

Macroscopically, a good sputum specimen consists of recently-discharged material from the bronchial tree, with minimum amounts of oral or nasal material. Satisfactory quality implies the presence of mucoid or mucopurulent material and is of greater significance than volume. Poor quality specimens are thin and watery or composed largely of bubbles. It is common practice in many TB diagnostic centres that sputum provided for AFB examination is first assessed macroscopically by laboratory staff. If the quality of the sputum is deemed inadequate, the specimen is rejected and the TB suspect asked to provide a new specimen. Providing sequential sputum specimens in a short period of time is considered difficult by many TB
suspects. The risk exists that the TB suspect will not return at a later stage to provide a sputum specimen leading to a missed opportunity for TB case finding.

A macroscopic assessment of specimen quality must be done by skilled laboratory staff involved but can be subjective.

Microscopic specimen assessment, in which smears are examined and graded according to an algorithm, has been proposed as a means to ensure sufficient specimen quality. Further specimens can be then requested if quality is inadequate. However, this is much more time consuming for the laboratory. There are several published algorithms for microscopic specimen assessment. Among the defined criteria, Murray & Washington, and Van Scoy, consider the specimens as saliva or sputum based on only the number of white blood cell (WBC) or epithelial cells (EPI) per low powered field (LPF). However, variations in the thickness of material in different areas of the slide may require extensive examination to obtain an overall average for each slide. To minimize the variability, the other two criteria (Barry and Gal-Oz) involve assessment of the ratio of WBC to EPI in several areas of the slide. It has been shown earlier that in the context of diagnosing respiratory infections the different microscopic criteria performed in a comparable manner.

These algorithms were developed to assess if it was worthwhile to culture a respiratory specimen. Using these algorithms for assessing the possibility for adequate AFB microscopy has been much less examined. A previous study on the usefulness of macroscopic assessment of respiratory specimens for AFB diagnosis was carried out in a routine TB diagnostic setting. This implies a passive case finding strategy in which individuals report themselves to a health facility because of symptoms. The current study is part of a TB prevalence survey which, by definition, entails an active case finding strategy in which individuals are approached and asked for symptoms. Investigators do not have the possibility to return to the individual at a later stage in such a setting. It is therefore pertinent that any decision on rejecting a specimen for investigation is made on solid arguments in this brief encounter. The objective of this study was to assess if these arguments should be based on macroscopic or microscopic assessment of respiratory specimens. Several countries will be embarking on similar large-scale TB prevalence surveys in the near future. The result of the present study will be able to guide field activities in these surveys in relation to the handling of submitted specimens.
Comparison of macroscopic & microscopic specimens

Methods

Setting and Population

The nation-wide TB prevalence survey was implemented during 2007-09 in which a representative sample size of 52,089 adults ≥15 years were divided over 40 (20 rural and 20 urban) randomly selected clusters. Each participating adult (15 years or older) provided two sputum specimens (one spot and one morning) regardless of symptoms during a household survey. The specimens were kept cool until transport to the field laboratory. Specimens were collected from several locations at the same time during the survey and arrived in a random fashion in the field laboratory. In this sub-study all survey participants who reported cough for 3 weeks or more were eligible for inclusion. The study was restricted to the last 21 clusters of the total 40 clusters for logistical reasons.

Field Activities

Each collected specimen was scored macroscopically as saliva or sputum by the trained field laboratory technicians at the time of arrival of the specimen in the field laboratory. Based on National Tuberculosis Control Programme guidelines, a specimen was considered saliva on visual assessment if it had a clear, watery appearance and contained no purulent material. Two smears from each of the fresh specimens (uncentrifuged) were prepared at the field laboratories, one for AFB and another for Gram staining. The slides prepared for Gram staining were heat fixed at the field laboratories and transported to the laboratory of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B). Specimens were refrigerated at the field sites and transported to the central laboratory for culture using conventional method within 48 hours of specimen collection. No preservatives were added.

Laboratory Activities

The prepared slide of the morning specimen of each enrolled individual in the sub-study was Gram stained. If there was no morning specimen available, the prepared slide of the spot specimen was used for Gram staining. Slides were stained with crystal violet and then treated with an I2-KI mixture (mordant) to fix the stain, washed briefly with 95% alcohol (destained) and finally counterstained with carbol fuchsin. The stained slides were examined under low-power (X100) magnification by the microscopist on duty. After examining 10 fields, two parameters were recorded: the average number of polymorphonuclear neutrophils (PMNs) and
squamous epithelial cells (SEC) per LPF. Four different algorithms (Table 1) were used for classifying a specimen as sputum or saliva based on microscopic features; (1) Murray & Washington: based on the average number of SECs; (2) Van Scoy: based on polymorphic cells; (3) Barry: based on epithelial and polymorphic cells; (4) Gal-Oz: Sputum quality was assessed by the presence of PMNs and SECs per LPF.

**Table 1:** Summary of four published criteria for judging Acceptability of Sputum Specimens

| Author          | Method                              | Criteria for Acceptability          |
|-----------------|-------------------------------------|-------------------------------------|
| Murray & Washington | Average no. of EPI/LPF             | <10 EPI/LPF                         |
| Van Scoy        | Average no. of WBC/LPF              | >25 WBC/LPF                         |
| Barry           | Assign + and – values, 3+ if >150 WBC/LPF; 2+ if 76-150 WBC/LPF; 1+ if 1-75 WBC/LPF; -3 if >25 EPI/LPF; -2 if 16-25 EPI/LPF; -1 if 5-15 EPI/LPF | Any positive score (sum of + and – values) |
| Gal-Oz          | Informative: <10 SEC/LPF & >25 PMNs/LPF; Semi-informative: <10 SEC/LPF or >25 PMNs/LPF; Uninformative: >10 SEC/LPF & <25 PMNs/LPF | (Semi) informative considered to be Sputum |

**Statistical Analysis**

The data were analyzed using SPSS v 17.0. The agreement between the scoring algorithms and macroscopic assessment was done by using the K (kappa) statistic, where the K value of > 0.4 was considered to be adequate concordance.

**Results**

Of the 901 specimens available in the study, we were able to obtain complete macroscopic and microscopic assessment data from 888 (98.56%). The quality of the remaining 13 slides was inadequate for proper reading.

Among the 561 (63%) macroscopically saliva specimens, 282 (51.4%) and 299 (54.5%) were classified as sputum by Murray & Wahington and Gal-Oz respectively. Among 340 (37%) specimens classified macroscopically as sputum, 187 (55.2%) and 198 (58.4%) were also sputum by both of the criteria. There was much poorer agreement between macroscopic assessment and the algorithms of Van Scoy and
Comparison of macroscopic & microscopic specimens

Barry (Table 2). All kappa statistics were below 0.1 indicating a very poor agreement between macroscopic and microscopic assessment of the specimens.

Table 2: Agreement between macroscopic and microscopic assessment of sputum specimens

| Sputum According to          | Saliva (n=561) | Sputum (n=340) | Kappa |
|------------------------------|----------------|----------------|-------|
| Murray & Washington          | 282 (51.4%)    | 187 (55.2%)    | 0.04  |
| Van Scoy                     | 2 (0.4%)       | 7 (2.1%)       | 0.02  |
| Barry                        | 126 (23.0%)    | 98 (28.9%)     | 0.06  |
| Gal-Oz                       | 299 (54.5%)    | 198 (58.4%)    | 0.04  |

All specimens in this sub-study were microscopically negative for AFB, but five of them were found to be positive on conventional culture. If culture of the specimens was conditional of the screening criterion used, then macroscopic assessment of the specimen would have missed one culture positive for TB, the microscopic criterion of Murray & Washington, Barry, and Gal-Oz two, and the criterion of Scoy all five.

Discussion

The use of Gram-stained smears to assess the quality of sputum specimens has received considerable attention as a means for improving the reliability of sputum microscopy as well as sputum culture for tuberculosis diagnosis. The evaluation of the quality of sputum using cytological parameters is very important but requires experience and qualification and is also time and resource-consuming.

This study showed that the agreement between macroscopic and microscopic assessment of sputum specimens was poor in the setting of an active case-finding strategy of a TB prevalence survey. Assuming the microscopic classification as a gold standard, this indicates that macroscopic assessment of provided specimens could not properly distinguish between saliva and sputum. In the national TB prevalence survey a total of 33 new smear-positive TB cases were detected among 52,089 population. Out of these 33 cases the morning sputum specimens collected from 19 (57.6%) were macroscopically classified as sputum whereas the remaining 14 (42.4%) were saliva. These two observations make that rejecting specimens based on the macroscopic assessment in this setting is not recommended since it will underestimate the prevalence of smear-positive specimens.
This study also showed that microscopic sputum assessment as a procedure did not contribute to the identification of specimens that were culture positive. Apparently it is more important that an actual specimen is submitted for sputum examination than that the submitted specimen is meeting specific macroscopic or microscopic qualities. From this it follows that survey personnel should be trained in obtaining specimens for subsequent microscopy, especially in patients who have difficulties in coughing up material. Recent studies showed that instruction given for a good quality sputum specimen increased both the quality and quantity of the sputum specimen with an increased positivity rate.\(^\text{13}\)

The poor performance of macroscopic assessment found in our study differs from the observation by Kahn \textit{et al.}, who stated that macroscopic assessment was a valid approach for identification of smear-positive respiratory specimens.\(^\text{9}\) This conclusion was based on the fact that macroscopic assessment rejected the least number of specimens in this study. As mentioned earlier, the main difference between the two studies is the setting, which indicates that operating procedures should be tested for validity in the setting they are being used rather than taken as face-value. Since the physicians are primarily responsible for submitting proper specimens to a laboratory, the use of the gram stain might be of some value in isolated instances where one needs to know whether specimens from patients suspected of having mycobacterial disease, but who have consistently negative smears and cultures, are of lower respiratory origin. In all other situations, including that of active case finding in a TB prevalence survey, efforts should be directed to obtain a specimen for processing.

These findings should be considered in the design of large-scale national TB prevalence surveys in other countries. Survey protocols tend to incorporate procedures derived from routine patient care. Without careful considering the different setting of the survey, this might lead to biased measurements in the field and the reporting of invalid prevalence estimates. This observation does not hold true only for TB prevalence surveys but can be considered for ongoing community surveillance systems in the field of respiratory disease in general.

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General Discussion

In 2007, the Bangladesh TB burden remained imprecise, mainly because of absence of a reliable notification system and any recently conducted survey. The currently used estimations are based on a World Health Organization (WHO) extrapolation in 1997, which was based on the disease and infection prevalence survey of 1964-66, conducted before DOTS era. Since the number of notified TB cases is not a good proxy measure for incidence or prevalence of disease, the national tuberculosis control programme (NTP) and international bodies, including WHO, expressed the need to undertake a nationwide disease prevalence survey along with an infection prevalence survey. This thesis reported the 2007-2009 national disease and infection prevalence survey results, and discussed changes in the forty five years since 1964-66 (Chapter 2 & 3). While the prevalence survey was conducted nationwide among the general population, data was also collected from a sample of passively detected TB cases in the DOTS centres, and from the general population on their care seeking for TB symptoms, their socio-economic position (SEP) and knowledge on TB in each survey cluster. In addition to prevalence estimates this thesis also focused on those findings in order to assess and understand the socio-economic as well as people’s perspectives about TB in the Bangladeshi community (Chapter 4-6).

Burden of disease

The 2007-09 national survey showed a much lower TB prevalence than earlier prevalence surveys (Chapter 2). The adjusted prevalence of smear-positive (SS+) TB in Bangladesh was 79.4 (95% CI: 47-134) per 100,000 people aged 15 years and over, which was 44% lower than the WHO estimation of 142 per 100,000 at that time. This low estimate has been questioned by different groups after publication. The World Health Organization, who commissioned the survey, is still not using the estimate, and has not shown any reflection on it so far, either in revising the disease burden in their own reports, or in any other communication. The NTP, who participated in conducting the study, also has not started to use this estimate in its policy or papers. The main argument for those questioning the results is the methodology used, in particular the absence of an initial screening for TB suspects (based on symptoms and x-ray abnormalities) before examining sputum specimens. At the time of the design of the survey and associated funding request, this approach was one of the four advocated by WHO, and the protocol used was therefore endorsed by WHO and the NTP of Bangladesh. Relying solely on the use of smear microscopy might under-estimate the prevalence of TB, as it misses all cases who are smear-negative but culture-positive. Examining sputum in the general population without culture as opposed to TB suspects, runs the risk of misinterpretation of smear-positive specimens caused by Mycobacteria Other Than Tuberculosis (MOTT), and therefore over-estimates the prevalence of TB. This risk is somewhat
increased by using fluorescence microscope for sputum examination rather than Ziehl-Neelsen (ZN) microscopy, as done in this survey. Lastly, it is often assumed that the large workload associated with sputum collection for all participants, rather than for suspects identified through screening, is associated with poor performance of smear microscopy. The risk related to wrongly identifying MOTT infections as smear-positive TB seems to be very minimal in the current survey since in almost 1000 specimens from the survey that were cultured in the context of the laboratory add-on study (Chapter 7), no MOTT was identified. The risk of poor performance of smear microscopy procedures was mitigated by having detailed standard operating procedures (SOP) for every steps of survey implementation, together with intensive training and very close monitoring throughout the survey period.

Given the time frame in which the survey needed to be concluded, the limited funding available, and the anticipated logistical problems in the country, employing both symptom screening and CXR as a screening step in the survey was deemed not feasible. A screening step in itself does not improve by definition the conduct of the survey, since it can result in missing of cases. In a survey conducted in Vietnam, just 11% of the suspect identified by symptom and X-ray screening had both symptoms and X-ray abnormalities, 60% had symptoms only and about 50% had X-ray abnormalities. Early screening by only symptoms or x-ray therefore would run the risk of missing suspected TB cases either way. The main purpose of the survey was to assess the prevalence of smear-positive TB in the community. A well conducted “sputum-examination-for-all” approach fitted better than an approach with a screening step.

The Bangladesh survey was implemented at a high standard, had a high participation rate, and external quality assurance revealed adequate laboratory procedures. Stringent quality control measures were followed including a laboratory based quality assessment of the sputum submitted. Participants were instructed how to provide the best possible specimen for examination. None of the provided specimens was discarded based on macroscopic appearance, resulting in a high rate of specimen submission. This proofed to be a good approach since an add-on study showed that in a setting of active case finding, judgment of the quality of submitted specimens by just macroscopic appearance was flawed (Chapter 7).

The survey population was representative of the general population in the country. As such it is fair to say that the survey indeed represents the current situation for smear-positive TB in the country. This was also the general consensus among TB programme implementers in Bangladesh, including the NTP Bangladesh and its NGO partners, who concluded during an international meeting that the TB burden had actually declined over the years. The stagnancy in case notification rate at 70/100,000 for SS+ cases for the last few years with a recent decline, despite major
efforts to identify more TB suspects who are assessed for TB, supports this result. Interventions to detect and treat TB cases by implementing DOTS since 1993, a very effective collaboration with NGOs, and parallel development in other non health sectors may have impacted on disease prevalence. An impressive cure rate was achieved during this period. This decline in smear-positive TB prevalence occurred in parallel with the decline of the other health problems like maternal mortality, and infant and child mortality though reasons for these declines may vary.\textsuperscript{9,10}

Despite the general decline in prevalence of smear-positive TB, there remain clear differences in prevalence between sex and setting. The higher prevalence among men than women is consistent with NTP notification and other local survey data.\textsuperscript{11-14} The sex difference persisted among all age groups in smear-positive cases as reported in the NTP annual reports, except for cases below 15 years of age, and cases with extra-pulmonary TB.\textsuperscript{11} Similarly, the higher prevalence among the rural than the urban population seen in the survey followed the notification pattern of the NTP. In 2007, 18.5\% of all cases were reported from urban areas that make up 28 \% of the country’s population.\textsuperscript{11,15} This lower notification could represent a lower prevalence of TB in urban areas as it was noticed that similar lower proportions of cases were detected from urban areas in the years 2008 to 2011.\textsuperscript{16-19} However, this might also partially be attributed to persistent poor case finding in urban areas. Delayed and lower coverage of DOTS in the urban areas, presence of excessive numbers of private practitioners not connected to the NTP, and fewer communication activities by the NTP might have contributed to a lower case notification in the urban settings. The recent finding of a higher prevalence of new smear-positive cases in urban slums indicates the presence of many undetected cases in urban slum areas, where NTP services are traditionally poor.\textsuperscript{20}

The tuberculin survey provided an estimate of the prevalence of infection and the Annual Risk of Tuberculous Infection (ARTI) among children up to 15 years of age. The current estimated prevalence of infection in 5-9 year old children was 10.0\%, as it was 17.9\% in the 10-14 years age group. The corresponding ARTIs were 1.5\% and 1.9\% respectively (Chapter 3). Comparing these data with the 1964-66 estimates in the 10-14 years group showed a very small decline of 1\% per year over a period of 45 years.\textsuperscript{21} A single estimate of the prevalence of infection or ARTI does not add much value to estimates of the TB burden in a country.\textsuperscript{22-24} Unfortunately, reliable additional data are absent in Bangladesh.

The first tuberculin survey conducted in 1964-66 still serves as the basis of all TB burden estimates in Bangladesh by WHO. But that survey suffered from some methodological drawbacks (including the use of low doses of antigen [1TU instead of 2 TU] resulting in low sensitivities, missing some of the remote clusters, and failing to read the reactions in time), making it difficult to compare the previous with
the current estimates. Several attempts to consolidate the data from this early survey provided different estimates. Begum et al. estimated a very low ARTI for those aged 5-9 years (0.61%) and 10-14 years (1.2%). Weyer totally ignored the data of 5-9 years considering the drawbacks of the survey reported, and the wide gap between unadjusted and adjusted results in this age group. She calculated the prevalence of infection for children aged 10-14 years to be 34.5% and the corresponding ARTI as 3.1%.

Bangladesh continues to have a high TB burden, according to the absolute number of annual incident cases (161,790 in 2012), with 66% of them being smear-positive, and less than 1% of the cases being below 15 years of age. However, uncertainty about the exact TB burden in Bangladesh continues to exist. The results of the recent survey do not seem to be able to guide the discussion on the burden of TB in the country at different national and international policy levels. Now, WHO is planning to undertake another national prevalence survey to be held in 2014. This new survey will include the WHO recommended methodology of initial symptom and radiological screening followed by bacteriological confirmation. This creates an opportunity to validate the findings of the 2007-2009 survey reported in this thesis. It is to be hoped that the sample size calculation takes the finding of the current survey into account in order to avoid an underpowered survey that in the end creates more confusion than that it tries to resolve. Furthermore, the new survey team needs to design proper strategies to mitigate unanticipated hindrances from adverse political and other social unrest.

For the longer term future, investing in a reliable and systematic notification system needs to be a high priority, as it would produce better estimates of incidence in the country, and be a better value-for-money. This can be further strengthened with periodical direct measurement of TB mortality from vital registration systems. Electronic and patient based data management systems will support timely and relevant monitoring of TB epidemiology on an ongoing basis.

**Outreach of NTP**

The TB prevalence survey collected for the first time information on wealth in the households of all participants. This was methodologically challenging considering the threat of compromising the conduct of the primary objective of the survey to assess the prevalence of smear-positive TB. However, the survey provided evidence that it was feasible both operationally and logistically. While maintaining the quality of the main objective, excellent data were collected from the households on their assets. The approach of assessing socio-economic position (SEP) for all participants in the survey made all non-TB cases a control for the identified TB-cases in the analysis of the relationship between prevalent TB and SEP. The size of the
control group could have been reduced if we would have chosen for a conventional nested case-control study in which a limited number of controls are sampled from the population at the time that a TB-case is detected. Although this would have markedly decreased the amount of work related to assessing SEP, it would have created some potential problems. In such an approach, controls would have been sampled after the study staff had visited the household and obtained participation. Returning to the household of the sampled control would run the risk of the control being absent or not willing to participate in a study procedure for the second time, both factors jeopardizing the validity of the SEP estimates in the control group. The validity could have been further influenced by sampling errors in the selection of controls. The chosen approach of assessing SEP for all made that throughout the survey, all survey staff conducted the same investigations in each of the households. In population surveys, such standardization of activities is of great importance in an attempt to minimize the risk of systematic errors. The study was able to show that the prevalence of TB was inversely associated with socio-economic position (SEP) and education (Chapter 4).

Poverty has been found to be strongly associated with TB, not only in disease occurrence but also in its progress and outcomes.\textsuperscript{30-33} This relation is mostly explained by the behavioural aspects of the poor in terms of delayed care seeking, late initiation of treatment, poor adherence to treatment, and inadequate follow up.\textsuperscript{34-38} The living conditions of the poor are in general conducive for TB exposure due to overcrowding,\textsuperscript{39} while the poor are also more susceptible to malnutrition and suffer social exclusion, which augments the risk for TB in this population.\textsuperscript{20} By comparing the SEP of the TB cases in the survey with those identified by the NTP, the survey showed clearly that the free DOTS programme of the NTP was not reaching all sections of the population equitably, thereby not reaching one of the main aims of DOTS programme. The data indicated that the poor, the less educated, and the worker class people bore the higher prevalence of the disease but were less likely to be detected by the NTP. This strengthens the argument that providing free services does not guarantee their utilization.\textsuperscript{30,40,41}

Bangladesh pursued a pro-poor socio-economic policy since independence in 1971, which now resulted in major changes in the population parameters. The poverty level declined by 26\% in a decade (2000-2010), and agricultural growth resulted in sustained food supply along with an increase in the population growth.\textsuperscript{42} Changes in health sector were also remarkable in attaining more equitable child survival, increased longevity at birth, and marked reduction in maternal mortality.\textsuperscript{9,10} Interventions like group micro finance, village pay phone, subsidized agriculture sector, free education for girls, and a dynamic NGO sector all played critical roles in this development. Indirect contribution of other non health sector developments like women empowerment, investments in infrastructures like power generation, roads
and communication, outstanding resilience against natural disasters, and enabling macroeconomic environment individually or all together are believed to have significantly contributed to this success.\textsuperscript{9,10,43}

The NTP initially cashed-in on this conducive environment by rapid expansion and attaining country coverage. However, the NTP needs to go further to address the remaining challenges of inequity in access to TB services by all sections of the population. The findings from the prevalence survey and accompanied studies together with the notification data highlight the programmatic aspects of the disease control that needs attention. The higher prevalence among the poor, uneducated, working class people, with the consistent static case notification for about a decade requires a proper response. The NTP needs in-depth analysis of its strategies to find innovative ways to maintain the good coverage as well as reach the currently unreached. Improved information, education and communication (IEC) strategies, alternative approaches to case finding (active, semi active), or specific strategies for targeted populations (urban, female, elderly population) should be considered.

\textit{Care utilization}

Care seeking for chronic diseases in Bangladesh has been shown to follow a rather fixed pattern: (i) initial care with informal sector, (ii) shopping between different care providers, and (iii) delay of varying duration before ending up with any formal care provider.\textsuperscript{33,34,44} Delay in initial care seeking for TB symptoms was well documented,\textsuperscript{34,45} but the pattern of care seeking at subsequent care seeking points was not known. The survey provided important insights by demonstrating that in most of the persons with TB symptoms, the initial care was with unlicensed providers, or non-specific home care (Chapter 5). A substantial proportion of individuals with TB symptoms remained with these providers for multiple rounds of care seeking.

These findings highlight the major role of the unlicensed informal care providers in the care seeking pathway of TB suspects, as reported earlier for other conditions.\textsuperscript{46,47} These unlicensed or informal care providers are the most thriving human resources in health sector in Bangladesh constituting more than 95\% of the total health workforce.\textsuperscript{48,49} People utilize their services for various reasons including low cost, easy accessibility, and possibility of getting services on credit.\textsuperscript{47,50} When the NTP is willing to acknowledge the role of these providers, it can engage them in TB-control measures by involving them in the programmatic activities. In fact, the WHO advocates “involving all providers” in TB control activities. However, the NTP should carefully consider all possible options and lessons available before getting involved with the informal care providers. Should the involvement be with or without regulation?; should there be any role of incentives?; at exactly what point of
care should they be involved? All these questions should be well thought of, as many such issues are not well evidenced yet. For example in Bangladesh, Damien Foundation (DF), an NGO working in partnership with the NTP, involved informal providers in referring suspected TB cases, and in providing directly observed treatment (DOT) in diagnosed cases with success, but only with a strong monitoring and supervision strategy throughout. Replication of this model (third party stewardship) by other NGO partners of the NTP so far did not show much success. The major constraint may be the lack of mutual trust among partners, and the absence of any simple realistic collaboration mechanism as most of the time the collaboration wanes off when the intervention finishes. A recent review on public private mix (PPM) approaches in tuberculosis concluded that a large component of the PPM has not been yet explored, including the issue of quality and equitable access to services. This is very important in Bangladeshi context where the majority of the poor TB cases access their initial services from the informal sector, while the quality of services provided by them is questionable.

Peoples’ care seeking decision and practice can be influenced by pre-existing knowledge about the disease, which in turn will be reflected in the outcome of the disease process. With case detection for TB being passive in Bangladesh, care seeking decisions impact on the formal case notification rate of the NTP. Identification of TB cases depends on the patient’s willingness to seek care and the choice where to seek care. It has been shown that care seeking is a complicated decision making process. It depends not only on the availability of services, but also on other factors like characteristics and quality of services provided, social status, and financial barriers. Knowledge on the seriousness of the condition and its impact on personal health might prompt health seeking for TB symptoms. For this reason, the NTP has been engaged in activities that have the aim to increase awareness of TB, and prompt care seeking at appropriate health care providers.

The survey showed that the awareness of TB, its transmission, and the availability of treatment was high in the general population (Chapter 6), but to what extent this good knowledge prompts proper care seeking is not known. Evidence from other sectors shows that this does not always happen. It seems that there are other barriers to seek care from appropriate care providers apart from adequate knowledge of the disease. Similar findings were reported in other countries like India and Vietnam. The role of knowledge in the care seeking process for TB remains therefore at best inconclusive. In this survey, the majority of the both actively and passively detected TB cases, initiated care at the informal sector and remained in that sector for four consecutive time and places [Chapter 6]. This disconnect between knowledge and care seeking needs to be carefully characterized and explored by the NTP before indulging into future interventions. Increasing TB knowledge should be coupled with strategies to improve proper care seeking. The NTP should identify
specific areas to be addressed, classify target audience and point out precise issues, language and messages to stimulate proper care seeking by those who need the service most.

**Laboratory Operational research**

The accuracy of the prevalence estimate in the survey depends on how well sputum specimens were collected, and smear examinations performed in the field. To assess the quality of the specimens submitted in this study the macroscopic and microscopic characteristics of the specimens were assessed (Chapter 7). The results indicated that the agreement between the microscopic and macroscopic assessment of sputum specimens was poor in the field setting. Many of the specimens classified as saliva were actually sputum according to various algorithms using microscopy. These algorithms are based on cytological examination of sputum with the different cut off points to decide based on the presence of white blood cells and/or epithelial cells per low powered field. Therefore it might be concluded that the macroscopic assessment of the quality of specimens is invalid in settings of active case finding. This finding will have consequences for the guidance issued by the NTP when embarking on alternative case finding approaches, as discussed above.

**Lessons learned**

There are many lessons learnt from the survey and its associated studies that have profound implications for the NTP. The prevalence of smear-positive TB has come down significantly from the previous estimates, based on a survey 45 years ago. Highly successful and quality DOTS implementation for about two decades may have contributed to this decline. At the same time it was also observed that prevalence remained 5 to 6 times higher among the poor, in the rural population, among males, and less educated persons. Especially the poor seem to be disconnected with the NTP given their marked under representation in the NTP case notification. This suggests that the NTP should not become complacent with the observed decline in prevalence but instead, re-assess its strategy for reaching the poor population that have the highest need.

The constraints of the poor to access the free DOTS services, and the continuous care seeking from the informal sector create a conducive environment for TB transmission, delayed initiation of treatment, DOTS bypass, and ultimately sustained presence of TB in the community. The studies presented in this thesis all provided evidence to support this statement. In order to bring the disease to a manageable state and to reach the Millennium Development Goals (MDG) and post MDG goals, the NTP should consider these factors and should develop strategies and innovative efforts immediately.
Future implications and research needs:

The continuous debate on the prevalence of TB in Bangladesh made that WHO felt the need to repeat a nationwide survey in 2014. This survey will not have a TB-infection component. To put the findings of the current TB-infection survey in perspective there is a need to design methodologies that address the limitations of the conventional tuberculin surveys. This could include use of new technologies like an Interferon Gamma Release Assay (IGRA) along with tuberculin, or repeat surveys in target areas to assess trends in ARTI. IGRA are less affected by MOTT or BCG status.

In Bangladesh, the impact of DOTS as a strategy at population level was never evaluated. Our study for the first time indicated that DOTS services are probably not being accessed by all groups of population equally, particularly by the poor, less educated and working class population. The high prevalence of TB in these groups also indicates ongoing transmission. The NTP should test innovative strategies to reach these groups of population in a more effective way than the current approach. Based on the findings of our surveys, the NTP has already commissioned studies to find out how equitably DOTS services can be extended to all by adopting strategies for active case finding in one area, and by semi active case finding in another area under a project called “translating research into action” (TRAAction). TRAAction is an USAID supported research initiative to undertake implementation research in areas of TB control, identified through national level workshops under auspices of NTP, Bangladesh. icddr,b is the implementing partner of the NTP and USAID in this initiative.

Our evidence on the complex pathways of care seeking, and status of knowledge among the TB cases and the general community pointed out several issues related with utilization of free DOTS services in the country. Some of the outstanding questions are: which factors shape care seeking pathways of TB suspects?; is the present state of knowledge adequate to initiate appropriate care seeking?; what should be the appropriate components of communication approaches that target urban, poor, illiterate or working class group of population?; how can the NTP address poverty related issues in its existing strategies?

The NTP of Bangladesh is committed to implement all components of the STOP TB strategy in its activities. Involving all providers is a major part of it. Our evidence definitely indicates that informal care providers play a very important role in the care seeking pathways of the TB suspects and TB cases. The pertinent question is how to reconcile their services in the existing systems without compromising the quality of TB-control. Prompted by the evidences produced by this survey, the NTP
has commissioned another study under the TRAction mechanism which is evaluating use of diagnostic algorithms and referral by the village doctors in a rural area of Bangladesh.

The studies presented in this thesis have instigated several research activities already underway and provided valuable evidences for the NTP to review its programme and future activities. The NTP organized an international workshop to discuss the issues related to the TB-prevalence survey. Several findings and recommendations of this workshop were translated in programme implementation, research activities, and proposal development under different funding procedures. One of the major issues identified by this exercise is to undertake in-depth analysis of the existing data of the NTP for future use (already commissioned to KNCV) and review of the existing programme. Digitization of the management information systems (MIS) is being piloted in some areas, while installing a continuous surveillance system to assess disease status is declared a priority. It is expected that the outcomes of all these activities will help the NTP to function more effectively to reach its goals.
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Samenvatting

Tuberculose is wereldwijd één van de belangrijkste oorzaken van ziekte en sterfte. In de laatste twee decennia heeft de ziekte aan miljoenen mensen het leven gekost. De Wereldgezondheidsorganisatie (WHO) heeft tuberculose in 1993 aangemerkt als een “noodtoestand” in een poging de verspreiding te beugelen. De aanbevolen strategie hiervoor is een aantal samenhangende preventieve en curatieve maatregelen samengevat onder de naam Directly Observed Treatment, Short course (DOTS). Bangladesh behoort tot de 22 landen in de wereld met de hoogste incidentie van tuberculose en voert sinds 1993 de DOTS strategie uit. De werkelijke omvang van de tuberculose-epidemie in Bangladesh is onbekend. Het is aannemelijk dat het aantal tuberculosepatiënten gerapporteerd in het nationale register te laag is, terwijl betrouwbare data van populatiestudies ontbreken. Dit proefschrift beschrijft studies naar de ziekteleast van tuberculose en tuberculose-infectie in Bangladesh. Daarnaast beschrijft het de sociaaleconomische aspecten van tuberculose, patronen van het gebruik van gezondheidszorg door tuberculosepatiënten en personen met klachten passend bij tuberculose, aanwezigheid van kennis over tuberculose in de algemene bevolking en de kwaliteit van sputumcollectie in een prevalentiesurvey.

De ziekteleast

Hoofdstuk 2 beschrijft de resultaten van de nationale tuberculose-prevalentiesurvey onder volwassenen (15 jaar en ouder). De survey is uitgevoerd tussen 2007 en 2009 met als doel een schatting te geven van de prevalentie van sputum-positieve tuberculose in Bangladesh. Van alle 52.098 deelnemers zijn 2 sputummonsters afgenomen welke zijn onderzocht met behulp van fluorescentiemicroscopie in het veldlaboratorium.

De prevalentiesurvey heeft 33 smear-positieve tuberculosepatiënten geïdentificeerd welke direct met een behandeling zijn gestart. De prevalentie van smear-positieve tuberculose in de volwassen bevolking van Bangladesh, gecorrigeerd voor studieopzet en uitval van participanten, was 79,4 per 100,000 (95% CI 47,1-133,8). De prevalentie was hoger onder mannen (121,7 per 100,000 [95% CI 69,6–212,8]) vergeleken met vrouwen (40,3 per 100,000 [95% CI 13,4–121,4]), in rurale gebieden (86,0 per 100,000 [95% CI 47,9–154,3]) vergeleken met urbane gebieden (51,1 per 100,000 [95% CI 27,7–94,1]), en onder personen met een lager opleidingsniveau. Schattingen van smear-negatieve tuberculose of extrapulmonale tuberculose zijn niet gemaakt.
Hoofdstuk 3 beschrijft de resultaten van de tuberculinesurvey welke was ingebed in de eerder beschreven prevalentiesurvey. De tuberculinesurvey is uitgevoerd onder kinderen in de leeftijd van 5-15 jaar. De aannemer is dat de prevalentie van tuberculose-infectie in deze groep een weerspiegeling is van de transmissie van de tuberculose in de algemene bevolking. De uitkomstmaat was de prevalentie van tuberculose-infectie en de hieraan gelieerde annual risk of tuberculous infection (ARTI). De tuberculinesurvey was de eerste na de enige andere survey uitgevoerd in 1964-1966. De survey is uitgevoerd onder 17.718 kinderen in de leeftijd van 5-14 jaar. De prevalentie van tuberculose-infectie is berekend met de mixture-method en de afkappuntmethode (8 mm of meer). De mixture method is gebruikt omdat deze het best onderscheid kan maken tussen huidreacties veroorzaakt door blootstelling aan mycobacterium tuberculose en reacties als gevolg van blootstelling aan andere mycobacteriën of BCG-vaccinatie. De afkappuntmethode is gebruikt om een direct vergelijk te kunnen maken met de methodologie die in 1964-1966 is gevolgd.

De mixture method resulteerde in een prevalentie van tuberculose-infectie van 10,0% en 17,9% in respectievelijk de leeftijdsgroep 5-9 jaar en 10-14 jaar. De corresponderende ARTI was respectievelijk 1,5% en 1,7%. De afkappuntmethode resulteerde in een infectieprevalentie van 12,4% en 22,6% in de leeftijdsgroepen van 5-9 jaar en 10-14 jaar, met een corresponderende ARTI van respectievelijk 1,9% en 2,1%. De tuberculinesurvey toonde een relatie aan tussen de prevalentie van tuberculose-infectie met blootstelling aan tuberculose (behorend tot een huishouden met een in de prevalentiesurvey geïdentificeerde tuberculosepatiënt), met een odds ratio (OR) van 4,5 (95%CI 1,7–11,9). De vergelijking tussen de huidige tuberculinesurvey en die van 1964-1966 toonde slechts een geringe afname van de prevalentie van infectie in de periode waarin Bangladesh uitgebreide tuberculose-controle maatregelen heeft geïmplementeerd. Echter, een periode van 45 jaar tussen de twee surveys is te groot om een betrouwbare trend te identificeren.

De gegevens over de ziektelast van tuberculose (ziekte en infectie) blijven moeilijk te interpreteren. Terwijl er een duidelijk afname is in de prevalentie van ziekte, die past bij de trend van een afnemend aantal geregistreerde patiënten, lijkt het erop dat de omvang van infectie in de populatie nauwelijks is afgenomen in de laatste 20 jaar waarin het tuberculose-programma is geïmplementeerd. Desondanks hebben de surveys waardevolle informatie voor het nationale tuberculose-programma van Bangladesh opgeleverd.
Reikwijdte van het nationale tuberculose-programma

Hoofdstuk 4 beschrijft de toegankelijkheid van de services welke geboden worden door het nationale tuberculose-programma. Een dergelijke analyse is niet mogelijk met de routinematig verzamelde notificatiedata. In de prevalentiesurvey van 2007-2009 is van alle 21.427 geselecteerde huishoudens informatie verzameld over de hun bezit van goederen, de structuur van het ondernemen en het gebruik van algemene services. Deze *assets data* geven gezamenlijk informatie over de sociaaleconomische positie (SEP) van het huishouden. Vergelijkbare data zijn verzameld van tuberculosepatiënten welke routinematig door het nationale tuberculose-programma zijn gediagnosticeerd in de clusters van de survey.

De prevalentie van tuberculose was vijf maal hoger in het laagste kwartiel van de populatie (95,4 per 100,000, [95% CI: 48,0-189,7]) vergeleken met de hogere kwartieren (19,5 per 100,000, [95% CI: 6,9-55,0]). De verdeling van SEP verschilde sterk tussen de tuberculosepatiënten gevonden in de survey en de tuberculosepatiënten gediagnosticeerd door het programma. Van de survey patiënten kwam 75,8% uit de twee laagste SEP kwartieren, terwijl 57,1% van de programma patiënten uit de twee hoogste SEP kwartieren kwam.

Deze bevindingen illustreren dat de prevalentie van tuberculose het hoogst is onder het meest arme deel van de bevolking, maar dat deze populatie minder gebruik maakt van de gratis services van het tuberculose-programma. Ondanks de grote nadruk op ontwikkelingsstrategieën voor de armen in Bangladesh, lijkt het erop dat het nationale tuberculose-programma de populatie mist die de services het meest nodig heeft.

Gebruik van gezondheidszorg

Hoofdstuk 5 beschrijft het gebruik van gezondheidszorg door survey patiënten en programma patiënten. Hiervoor zijn tuberculosepatiënten geïnterviewd met gebruik van gestructureerde vragenlijsten. De studie had als doel het in kaart brengen van het traject van het gebruik van gezondheidszorg voor klachten passende bij tuberculose. Daarnaast inventariseerde de studie de handelingen van de zorgverleners bij patiënten met dergelijke klachten. Van de in totaal 273 patiënten waren er 33 geïdentificeerd in de prevalentiesurvey en 240 steekproefsgewijs geselecteerd uit de programmaregisters in de clusters van de survey.
Alle survey patiënten startten hun zorgtraject met het bezoeken van niet-specifieke zorgverleners of met zelfzorg (huis-tuin-en-keuken middelen of traditionele behandelingen). De meerderheid (82%) keerde tenminste vier keer op rij terug bij deze vorm van zorg. Bijna de helft (49%) van de programma patiënten startten hun zorgtraject met een bezoek aan een informele zorgverlener. Van hen keerde 44,0%, 14,4% en 4,2% respectievelijk twee, drie of vier keer op rij terug bij deze vorm van zorgverlener. Bij alle zorgverlener werd voornamelijk medicatie voorgeschreven, terwijl patiënten niet of nauwelijks werden verwezen voor advies of verdere diagnostiek.

Deze bevindingen onderstrepen de belangrijke rol die informele zorgverleners in Bangladesh spelen in het zorgtraject van personen met klachten passend bij tuberculose. Dergelijke zorgverleners zouden betrokken moeten worden bij de activiteiten van het nationale tuberculose-programma om zo bij te dragen tot een verbeterde identificatie en behandeling van tuberculosepatiënten.

Kennis over tuberculose kan een belangrijke factor zijn in beslissingen omtrent het initiëren en de vorm van het zorgtraject. Hoofdstuk 6 beschrijft de kennis over tuberculose onder tuberculosepatiënten en een steekproef van de algemene bevolking. Deze studie maakte gebruik van de eerder beschreven 240 programma patiënten, aangevuld met 240 personen geselecteerd uit huishoudens in de prevalentiesurvey. De interviews lieten over het algemeen een grote kennis over tuberculose zien op verschillende gebieden (symptomen, transmissie, preventie, behandeling). Echter, de kennis was lager bij de algemene bevolking in vergelijking met de tuberculosepatiënten, zowel op het gebied van transmissie (80% versus 88%), manier van transmissie (67% versus 82%), kennis van andere tuberculose symptomen dan hoesten (78% versus 89%), genezingskans (90% versus 98%) en beschikbaarheid van gratis behandeling (75% versus 95%). Parameters van kennis werden samengevat in een knowledge score, waarna bleek dat personen uit de algemene bevolking drie keer grotere kans op “slechte” kennis hadden in vergelijking met tuberculosepatiënten (OR 3,46, [95% CI: 2,00-6,09]).

Deze bevindingen geven aan dat tuberculosepatiënten ingezet zouden kunnen worden als peer educators bij het nationale tuberculose-programma met als doel het verbeteren van de communicatie tussen programma en de algemene bevolking. Dit ter verbetering van de identificatie en behandeling van patiënten.
**Samenvatting**

**Laboratorium**

**Hoofdstuk 7** beschrijft de resultaten van een laboratoriumstudie die is uitgevoerd in de context van de prevalentiesurvey. De studie had als doel om te beoordelen of de kwaliteit van de monsters kon worden vastgesteld door middel van alleen een visuele inspectie. Gezondheidswerkers in een klinische setting vertrouwen vaak op een dergelijke beoordeling voor het identificeren van monsters die geschikt zijn voor een kweekonderzoek. In het kader van een prevalentiesurvey (waar weinig deelnemers klachten hebben) is het van belang om een goede kwaliteit van monsters te hebben zodat laboratoriumtesten adequaat kunnen worden uitgevoerd. In deze studie zijn monsters van 901 personen met hoestklachten voor meer dan twee weken steekproefsgewijs geselecteerd. Medewerkers van het veldlaboratorium classificeerden het monster als sputum of niet, gebaseerd op macroscopische inspectie. Daarna werden de monsters naar het centrale laboratorium vervoerd waar formele classificatie plaatsvond op basis van microscopische parameters (Gram kleuring). Alle monsters werden gekweekt voor tuberculose.

Uit de resultaten bleek dat er een slechte correlatie was tussen macroscopische en microscopische parameters van de monsters. Monsters die in het veld niet als sputum werden geclassificeerd waren dat in 30-60% van de gevallen wel (afhankelijk van het microscopische algoritme).

De bevindingen geven aan dat in een prevalentiesurvey het van belang is dat alle monsters worden beoordeeld ongeacht de macroscopische interpretatie van de kwaliteit van het monster. In plaats daarvan zijn stringente kwaliteitsprocedures van belang zodat het beste monster van de deelnemers wordt verkregen.

**Discussie**

**Hoofdstuk 8** beschrijft de synthese van de resultaten uit alle eerder beschreven hoofdstukken, de implicaties die deze gegevens hebben voor activiteiten van het tuberculose-programma van Bangladesh en de prioriteiten voor verder onderzoek.
Summary

Tuberculosis (TB) is one the major causes of sickness and deaths among adults worldwide. The disease caused millions of sufferings and deaths in the last two decades, and a global emergency was declared by the World Health Organization (WHO) in 1993 to control its expansion. Directly Observed Treatment, Short course (DOTS) is a package of curative and preventive strategies advocated by WHO to diagnose and treat TB cases in an effort to attain TB control globally. Bangladesh, one of the 22 high TB burden countries in the world, adopted and started implementing DOTS since 1993. The true burden of disease in the country is not exactly known. National notification data have the limitation of being vulnerable to underreporting of TB cases, while reliable data from national surveys are absent in the country. In this thesis, we presented studies on the TB burden in Bangladesh in terms of prevalence of the TB disease, and the prevalence of the TB infection. In addition we described the social aspects of TB, care seeking behaviour of TB cases and persons with symptoms suggestive for TB, knowledge on TB-related issues in the community, and the quality of field level sputum collection procedures in the prevalence survey.

The burden of disease

In chapter 2 we reported the national TB disease prevalence among adults (15 years and above). This prevalence estimate was obtained through a nationwide cross sectional household survey which was carried out during 2007-2009. The aim of the survey was to determine the prevalence of sputum smear-positive TB in Bangladesh. We collected two sputum samples from each of the 52,098 participants who consented to participate. Sputum samples were examined at field laboratories with fluorescence microscopy. A total of 33 smear-positive TB cases were diagnosed among the person examined and were put under treatment. The overall prevalence in the population aged 15 years and over after adjustment for study design and attrition was 79.4 per 100,000 (95% CI 47.1-133.8). The prevalence was higher in males (121.7 per 100,000 [95% CI 69.6–212.8]) compared to females (40.3 per 100,000 [95% CI 13.4–121.4]), in rural areas (86.0 per 100,000 [95% CI 47.9–154.3]) compared to urban areas (51.1 per 100,000 [95% CI 27.7–94.1]) and among person with a lower level of education. The survey did not include persons below 15 years, and did not identify sputum smear-negative or extra pulmonary TB cases.

In chapter 3 we reported the prevalence of tuberculous infection and its associated Annual Risk of Tuberculous Infection (ARTI). The estimate was obtained by including a tuberculin survey in the national TB prevalence survey. The prevalence of TB infection is traditionally measured among children (5-14 years) with the assumption that it is reflecting the magnitude of recent transmission. The risk of
infection in the general population is deducted from this prevalence of infection in children and expressed as ARTI. The tuberculin survey was the first one after the only other tuberculin survey conducted in 1964-66. This was a multi-staged community-based, cross-sectional survey including 17,718 children below 15 years. The prevalence of infection was estimated by using the mixture method and the cut-off method (with a cut-off point of ≥ 8 mm). The mixture method was used because it is the best methodology to dissect skin reactions due to exposure to Mycobacterium tuberculosis or reactions due exposure to other mycobacteria or BCG vaccination. The cut-off method was used to mimic the approach used in the 1964-66 tuberculin survey. The prevalence of infection was 10.0 % and 17.9 % in 5-9 years and 10-14 years respectively with corresponding ARTI was 1.5% and 1.7% according to mixture analysis. This was 12.4 % and 22.6 % in 5-9 years and 10-14 years respectively using a cut-off point ≥ 8 mm. The associated ARTI for 5-9 and 10-14 years was 1.9% and 2.1%, respectively. The study showed a relation between the prevalence of infection and TB exposure (belonging to a household with a TB case identified in the survey), with an odds ratio [OR] for exposure of 4.5 (95%CI 1.7–11.9). Comparing the data from the current tuberculin survey with those from the 1964-66 survey showed only a moderate reduction the prevalence of infection for the two decades in which TB control activities were implemented, although the interval of 45 years between the two surveys is too large for a reliable estimate of the trend in the prevalence of infection.

The data on the burden of TB in Bangladesh remains difficult to interpret. While there is a clear decline in the prevalence of active disease, which fits the notification data, the burden of infection seems to have changed very little over the past 20 years. Despite this, the two surveys provided valuable information for the management of TB control by the NTP of Bangladesh.

**Outreach of the National Tuberculosis Programme**

In chapter 4 we assessed whether access to TB control activities of the NTP, including free DOTS service, is equitable with respect to socio economic position (SEP). This analysis addressed the lack of information on TB notification or TB prevalence data segregated by SEP. The prevalence survey from 2007-09 had the unique feature of collecting assets information from all the participating 21,427 households. Similar data were collected from a sample of TB case detected routinely under the DOTS programme of the NTP from the same cluster where the survey was carried out. We compared the SEP of the case detected under survey (active case detection) and that of the cases under DOTS (passive case detection). The prevalence of tuberculosis was five times higher in the lowest SEP quartiles of population (95.4 per 100,000, [95% CI: 48.0-189.7]) to highest SEP quartile population (19.5 per 100,000, [95% CI: 6.9-55.0]). The SEP distribution for the two types of TB cases
differed markedly. Among the survey cases, 75.8% were from lower two quartiles; while among cases under NTP, 57.1% were from uppermost two quartiles of the population. These findings indicate that TB prevalence is highest among the poor, while at the same time the poor are accessing the free DOTS services available through the country less often than individuals with the highest SEP. Despite a large emphasis of pro-poor development strategies, the NTP seems to miss those populations that need its service most.

**Care utilization**

In chapter 5 we described the care seeking behaviour of both actively identified TB cases in the survey and passively identified cases by the NTP. In total 273 TB cases were interviewed using structured questionnaires. The main aim was to assess trajectories of care-seeking, and services received at specific points of care. Of the included cases, 33 were actively detected under survey and 240 were sampled randomly from the passively detected cases under NTP by its routine DOTS programme from registers in the same clusters as where the survey took place. All the 33 actively detected case initially sought non specific care, or self-care (home remedies or traditional treatment). The majority of them (82%) remained with no care or self-care up to fourth subsequent point of care. From the passively detected cases, 118 (49%) initiated care seeking by visiting an informal provider. Of those 52 (44.0%), 17 (14.4%) and 5 (4.2%) remained in that informal care sector at second, third and fourth subsequent points of care. Prescription of medication was the principal care provided by any of the providers. Patients were very seldom referred for advice or investigations. These findings highlight the important role of informal providers in the pathway of diagnosis and treatment of persons with TB symptoms in Bangladesh, and the need to involve all types of care providers in TB-control activities for improved case detection by the NTP.

Knowledge of TB could be an important factor in not only care seeking decisions, but also in decisions on the initiation of treatment, and treatment compliance. In chapter 6 we described the knowledge on TB among a sample of newly diagnosed TB cases and controls from the general population. This study included 240 TB cases from the TB registers from the 40 clusters where the national prevalence survey was implemented and 240 adult individuals randomly selected from the households under survey. All participants were interviewed using a structured, pre tested questionnaire. Although the results showed overall a large knowledge on major aspects of TB (symptoms, transmission, prevention, treatment), the community controls showed poorer knowledge in some areas compared to TB cases, including TB transmission (80% vs.88%), mode of transmission (67% vs. 82%), knowing other symptoms than cough (78% vs. 89%), curability of TB (90% vs. 98%) and free availability of treatment (75% vs. 95%). Overall knowledge was explored by creating
a “knowledge score”. After controlling for other factors in a multivariable model, community controls had more than three times (OR 3.46, [95% CI: 2.00-6.09]) more often poor knowledge compared to the TB cases. This shows a potential opportunity of use of TB cases as peer educators by the NTP in its efforts to communicate more effectively TB-control strategies and messages to improve care seeking of TB suspects in the community.

In chapter 7 we described the results of a laboratory add-on study to the national TB prevalence survey. It evaluated the validity of judging the quality of submitted specimens by macroscopic assessment. Such evaluation is often done in the clinical setting to identify specimens to be sputum and suitable for culture. The accuracy of measuring the prevalence of smear-positive TB in a field situation depends on the quality of specimens submitted by the participants (who in the large majority do not have any symptoms). This study examined randomly selected specimens from 901 participants with a cough for more than 2 weeks in the prevalence survey. The field staff was asked to classify the specimens as sputum or saliva based on macroscopic features. The samples were transported to the central laboratory where they were assessed against four known algorithms for classification of specimens based on microscopic features (Gram stain). All submitted specimens were cultured for TB. The results showed a very poor correlation between the macroscopic classification and the microscopic characteristics of the specimens. Specimens categorised as saliva in the field were actually sputum in 30% to 60% of the times, depending on algorithm used. This implies that in a field setting of a prevalence survey, macroscopic assessment is of no value for judging the quality of specimens provided. All specimens should therefore be submitted for examination. In the survey setting there is a need for stringent quality assurance procedures for specimen collection and handling instead. Such procedures were present throughout the survey in Bangladesh.

In chapter 8 we combined the findings from the previous chapters and discussed their implications for future TB-control in Bangladesh. We identified research needs and priority areas for strengthening activities from the NTP.
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Brothers at Huize St. Jozef, Westeinde 101, 2512 GW The Hague

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Curriculum Vitae

Shahed Hossain was born on June 08, 1954 in Khulna, Bangladesh. He received his Bachelor of Science in Medicine (MBBS) from Rajshahi Medical College in 1980. During 1981 to 1994 he served as medical officer to different positions under public health sector, Bangladesh. In 1995 he completed M.Sc in Health Development and an MBA on Health Management from Chulalongkorn University, Thailand. In 1996 to 2000, he served as a national management consultant for TB control for WHO, Bangladesh. He joined icddr,b in 2000 as an Associate Scientist and since then he is involved in different research projects.

During 2007-2011, when the National Tuberculosis Control Programme (NTP) implemented the national disease cum infection prevalence survey, he became the Co-principal investigator of the study. He started working closely with KNCV tuberculosis foundation, the technical partner of NTP, Bangladesh in conducting the survey. His PhD works were undertaken under the auspices of KNCV, under the supervision of Prof. Dr. Martien Borgdorff and Dr. Frank van Leth from University of Amsterdam and Dr. K. Zaman from icddr,b. KNCV facilitated him to participate in several short courses on statistics (2011) and use of statistical packages (Stata) in the interim period (2013). His works with KNCV on National Tuberculosis Prevalence Survey are presented in this thesis.
