Tuberculosis burden in Bangladesh: epidemiological estimates and people’s perspectives
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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.³ 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.⁶ 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.⁷ 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.⁸ 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%).25 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%.26

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.27 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.4,28 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.29 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 conductive 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.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.

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.33,34,44 Delay in initial care seeking for TB symptoms was well documented,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.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.48,49 People utilize their services for various reasons including low cost, easy accessibility, and possibility of getting services on credit.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.\textsuperscript{51} 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\textsuperscript{44,52} 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.\textsuperscript{53} 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.\textsuperscript{54,55} 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.\textsuperscript{56-59} The role of knowledge in the care seeking process for TB remains therefore at best inconclusive.\textsuperscript{33,56-59} 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” (TRAction). TRAction 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.
References


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