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First Bangladesh National Tuberculosis Drug Resistance Survey 2010–2011

Ministry of Health and Family Welfare
Directorate-General of Health Services
Mycobacterial Disease Control
National Tuberculosis Control Programme

World Health Organization
Country Office for Bangladesh

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FROM THE AMERICAN PEOPLE

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Acknowledgements

It is my pleasure to pay tribute to the Government of Bangladesh, especially the Ministry of Health and Family Welfare, for its commitment to conduct the **First Bangladesh National Tuberculosis Drug Resistance Survey (2010–2011**) and for its understanding, as a high burden country, of the problem of drug resistance among tuberculosis (TB) patients.

The National Tuberculosis Control Programme (NTP) established the National Tuberculosis Reference Laboratory (NTRL) in 2007 at the National Institute of Diseases of the Chest and Hospital (NIDCH) as the key organization for conducting drug resistance surveys. In the Stop TB Strategy, the World Health Organization (WHO) incorporated multidrug-resistant (MDR) TB in the NTP programme. In this context, the Green Light Committee approved the NIDCH project for treating MDR-TB patients in 2008. Bangladesh is one of the high MDR-TB burden countries, but there were no national data on the actual number of drug-resistant cases in the country. This hindered country planning and fund mobilization. To mitigate this obstacle, the Director of Mycobacterial Disease Control and Line Director for TB-Leprosy with his team made extensive efforts to ensure the effective conduct of this survey with nongovernmental organization (NGO) collaboration. NTP leadership was crucial to conduct this unique multisectoral study. WHO Bangladesh, with support from the WHO Regional Office for South-East Asia, played an appreciable role, including the development of protocols, procurement and supply of logistics, supervision, monitoring, and finance regulation.

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Institutes/organizations that commissioned the study and their roles

(1) Ministry of Health and Family Welfare: Government commitment.

(2) National Tuberculosis Control Programme: Commitment, initiation, fund mobilization, country coordination, health worker training, monitoring and evaluation, development of training module.

(3) World Health Organization: Development and approval of protocol, supply management, health worker training, arranging external technical assistance, monitoring and evaluation, assisting coordination with all stakeholders, development of training module, data analysis and report writing.

(4) National Tuberculosis Reference Laboratory: Protocol development, training module development, drug resistance survey kit preparation and supply, overall coordination, culture and drug susceptibility testing, Supranational Tuberculosis Reference Laboratory coordination, monitoring and evaluation, data entry, recording and reporting, health worker training, disbursement of research assistant fees, etc.

(5) National Institute of Diseases of the Chest and Hospital: Continuous support to the National Tuberculosis Reference Laboratory, monitoring and supervision, administrative help.

(6) Supranational Reference Laboratory Antwerp, Belgium: Technical assistance, onsite visits, rechecking drug susceptibility test results of National Tuberculosis Reference Laboratory, mycobacteria other than *Mycobacterium tuberculosis* confirmation, fingerprinting of selected strains.

(7) Bangladesh Medical Research Council: Ethical clearance.

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(9) Health-care facilities (*upazila* health complexes and chest disease clinics): Data collection, microscopy, sample collection and shipment and coordination.

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Message from the Country Coordinator

Under the overall guidance of the National Tuberculosis Control Programme (NTP), the National Tuberculosis Reference Laboratory (NTRL) in collaboration with WHO, Damien Foundation, BRAC Health Programme, Supranational Reference Laboratory (SRL), a Belgium, nationwide TB drug resistance survey has been carried out in representative samples of newly diagnosed smear-positive cases. The overall goal of this survey was to strengthen the detection and monitoring of levels for anti-TB drug resistance among TB patients and to improve the efficiency of TB control in Bangladesh. In 2010-2011, the NTP carried out its first nationwide drug resistance survey (DRS) in new and retreatment TB patients as part of the WHO and International Union Against Tuberculosis and Lung Disease global network for surveillance of drug resistant TB.

TB is a major public health concern in Bangladesh affecting not only patients but also their families and the community as a whole. It is listed among the 22 high TB burden countries and the 27 high burden MDR-TB countries. The political commitment is manifested in maintaining human and financial resources for successful implementation of the TB control programme in Bangladesh. The NTP's Strategic Plan to Control TB, 2011-2016 is in line with the WHO's Stop TB Strategy.

One of the aims of ensuring effective management of TB is to minimize the development of drug resistance. Surveillance of anti-TB drug resistance is, therefore, an essential tool for monitoring the effectiveness of TB control programmes and improving national and global TB control efforts. No nationally representative drug resistance data were available in Bangladesh before this DRS. From this DRS data it has been shown that levels of drug resistance in Bangladesh are low, with 1.4% among new MDR-TB cases and 28.5% among retreatment cases.

The data provided by this survey will contribute to a better understanding of the national and international situation of TB drug resistance.

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Acronyms

AFB	acid-fast bacillus/bacilli
BRAC	Bangladesh Rural Advancement Committee
CDC	chest disease clinic
CI	confidence interval
CLs	confidence limits
CPC	cetylpyridinium chloride
DOTS	directly-observed treatment (short-course)
DRS	drug resistance survey
DST	drug susceptibility testing
EQA	external quality assurance
GDP	gross domestic product
ICDDR,B	International Centre for Diarrhoeal Disease Research, Bangladesh
MBDC	Mycobacterial Disease Control
MDR-TB	multidrug-resistant tuberculosis
MOTT	mycobacteria other than tuberculosis
NIDCH	National Institute of Diseases of the Chest and Hospital
NGO	nongovernmental organization
NTP	National Tuberculosis Control Programme
NTRL	National Tuberculosis Reference Laboratory
OR	odds ratio
PMDT	Programmatic Management of Drug-Resistant TB
SRL	Supranational Reference Laboratory
TB	tuberculosis
UH&FPO	*Upazila* Health and Family Planning Officer

URC	University Research Co., LLC
USAID	United States Agency for International Development
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Executive summary

Objective: The general objective of this survey was to strengthen the detection and monitoring for anti-tuberculosis (TB) drug resistance among TB patients in Bangladesh.

Study design: The study was cross-sectional, targeting all new and previously treated smear-positive TB patients.

Sample size and selection of sample: The total sample was 1080 new smear-positive patients. In addition, specimens were collected and tested from previously treated cases registered in the selected cluster as well as in the chest disease clinics (CDCs) located in the same district as the selected cluster during the period that new patients were included. However, CDCs were asked to send previously treated cases throughout the year. In total, 40 clusters including two subclusters and 34 CDCs/districts were selected for the study.

Methodology: The duration of the project was 12 months (December 2010 to November 2011). During this period a total of 1480 TB patients were interviewed, who included both new and retreatment cases. Of all TB patients, 70.8% were male and 75.6% had an income level less than 7500 Taka (US$ 97). The majority of patients enrolled (85.9%) lived in non-metropolitan areas and a quarter (25%) were farmers.

Among the 1480 smear-positive samples, identical strains were found in 12, and thus the final number of eligible patients was 1468. Of these, 96 (6.5%) had a negative culture, 13 (0.9%) had culture contaminated, 11 (0.9%) were infected with mycobacteria other than tuberculosis (MOTT); thus 1348 (91.8%) had positive cultures. Five of these (0.4%) had no interpretable drug susceptibility testing (DST) results, leaving 1343 of eligible patients (91.5%) with valid DST results. The vast majority of the 1049 (78.1%) patients enrolled were new smear-positive cases of TB and the remaining 291 (21.7%) were previously treated cases.

Results: Of the total of 1049 new TB cases tested, 88% were infected with pan-susceptible strains, i.e. those susceptible to all four first-line anti-TB drugs (95% confidence interval (CI) 84.0–90.7). Prevalence of multidrug resistant (MDR) TB among new cases was 1.4% (95% CI 0.7–2.5) and total mono-resistance in new cases was 8.4% (95% CI 5.9–11.9). However, mono-resistance to rifampicin and isoniazid was 0.2% and 1.4%, respectively and the total poly-resistance was 2.5% (95% CI 1.6–3.9).

Of the 291 previously treated TB cases tested, 56.8% were infected with pan-susceptible strains, i.e. those susceptible to all four first-line anti-TB drugs (95% CI 50.5–62.9). Prevalence of MDR-TB among these cases was 28.5% (95% CI 23.5–34.1). Total mono-resistance in previously treated cases was 10% (95% CI 7.3–13.5). However, mono-resistance to rifampicin and isoniazid was 0.4% and 2.5%, respectively and the total poly-resistance was 4.7% (95% CI 2.6–8.5).

All variables recorded (age, sex, history of TB treatment, and place of residence) were included in the univariate and the multivariate analyses. As expected, history of previous anti-TB treatment was the strongest independent factor for any drug resistance odds ratio (OR 29, 95% CI 15.9–53.0) and MDR-TB (OR 34.9, 95% CI 18.5–65.8). In addition, the univariate analysis showed that living in metropolitan areas increased the risk of any drug resistance (OR 2.5, 95% CI 1.4–4.6) and MDR-TB (OR 0.7, 95% CI 0.4–1.2). Logistic regression analysis showed that factors such as age, sex, occupation, and income had no effect on drug resistance in TB patients except in the age group below 45 years, which showed significantly higher MDR rates ($p<0.05$). However, no extensively drug-resistant (XDR) TB was isolated during the survey.

Conclusion: The prevalence of MDR-TB in new cases (1.4%) was lower than estimated, but the prevalence of MDR-TB in previously treated cases (28.5%) was much higher. Although the rate is low compared with other countries, the high TB prevalence in the community will reflect a high overall burden due to MDR-TB. The data gleaned during the survey validate the study and show that the TB control programme is running effectively in the country.

1. Introduction and background information

1.1 Country profile

Bangladesh is a developing country situated in South-East Asia. It has a population of over 155 million[1] making it one of the most densely populated countries in the world. TB is a major problem, affecting not only patients but also their families and society as a whole. TB control is recognized as crucial for poverty alleviation and for overall development of the country.

Bangladesh is administratively divided into 6 divisions, 64 districts, 6 metropolitan cities, 508 *upazila* (subdistricts), and 4466 unions. It is one of the least developed countries with a gross domestic product (GDP) of US$ 482 per capita in 2006,[2] where 49% of the population live below the poverty line. The literacy rate is 50%. Urbanization is increasing with approximately 23% of the population now living in urban areas.

Children aged under five years represent 12% of the population and 15–59 year olds comprise 55%. The annual population growth rate was 1.4% as per 2001 census data. In 2006 the infant and maternal mortality rates were 52.0 and 3.7 per 1000 live births, respectively. In the same year the crude death rate was 5.8 per 1000 population while the life expectancy at birth was 65 years. Communicable diseases (including TB) are major causes of morbidity and mortality.

1.2 Tuberculosis

TB is an infectious disease caused by *Mycobacterium tuberculosis*. The disease can affect every organ in the human body, although it mostly affects the lungs.

M. tuberculosis is a rod shaped microorganism that can be detected by the Ziehl-Neelsen staining method, and is called acid-fast bacilli (AFB). The bacilli can remain alive for several hours in a dark and moist surrounding, but quickly perish in direct sunlight. In the body, they can remain dormant and persist for many years.

Transmission occurs by infectious droplets, when a person with TB coughs or sneezes. In the human body, the bacilli will spread through the lymphatic and blood circulation system or directly spread to the target organs. The most effective prevention method is to identify TB cases as early as possible, especially the sputum smear-positive cases, and provide them with adequate treatment until they are cured. Transmission can be prevented by covering the mouth while coughing or sneezing. Good ventilation will help reduce indoor TB transmission. Health education can also help to reduce TB transmission. The benefit of Bacillus Calmette–Guérin (BCG) vaccination is to protect young children against disseminated and severe TB, especially in high prevalence areas.

TB treatment is lengthy and consists of isoniazid (H), rifampicin (R), ethambutol (E), pyrazinamide (Z), and streptomycin (S). The patient should take the drug regularly until pronounced cured. The present short-course TB regimen contains four anti-TB drugs in the initial phase, one of which is rifampicin. The directly-observed treatment short-course (DOTS) strategy in Bangladesh contains two short-course TB regimens.

- Category 1: 2(HRZE)/4(RH) to be administered to new sputum (+) pulmonary TB cases, sputum (–) pulmonary TB cases with extensive parenchymal involvement, and severe forms of extrapulmonary TB.
- Category 2: 2S(RHZE)/1(HRZE)/5(HRE) to be administered to smear (+) previously treated TB cases. The NTP has now adopted the Green Light Committee regimen for treatment of drug-resistant TB.

1.3 Drug-resistant tuberculosis

TB drug resistance occurs when inappropriate anti-TB drugs are used for treatment. Since the early 1990s, several outbreaks of MDR-TB have been reported in different regions of the world as a consequence of such inappropriate use. MDR-TB usually occurs in chronic cases, although a small proportion is seen in new TB cases. TB drug resistance surveillance is needed to detect its magnitude, especially in countries where anti-TB drugs are applied inappropriately to treat TB cases. To this end, there is a need to establish surveillance of drug resistance in the world to obtain data that are standardized and comparable. The World Health Organization (WHO) has initiated a global surveillance programme through its collaborating centres for MDR-TB.

Drug resistance is becoming a more important barrier to effective treatment of TB, and threatens the effectiveness of NTPs. High levels of resistance can particularly be found in parts of Asia, Eastern Europe and Africa.[3,4] Potential causes of drug resistance include: inadequate treatment regimens available from health providers; ineffective case holding; unreliable drug supply; poor quality of drugs; patient errors in following the prescribed regimens; and misuse of anti-TB drugs in the private sector. The most important cause of development of drug resistance may well be errors in prescribing the correct regimen, particularly related to high levels of primary drug resistance. High levels of rifampicin resistance, for instance, may require adjustment of the standardized treatment regimens used by the control programme to guarantee high cure rates.

In 1994, WHO initiated a global project with the aim of estimating the global burden of drug-resistant TB worldwide using standardized methodologies, so that data could be compared across and within regions. The global project is based on random sampling of patients reporting to national TB programmes. Susceptibility testing is performed by reference laboratories according to an agreed technique. As a first step, a regional survey in 10 Latin American countries was carried out. The overall experience gained suggested that a sample survey of drug resistance with failure rates of more than 5% might indicate inadequate routine treatment and high levels of initial

resistance. This makes a survey of anti-TB drug resistance an urgent priority and an important tool to define its magnitude, especially in countries with a high burden of disease and an evolving medical system.

1.4 Epidemiology of tuberculosis in Bangladesh

Bangladesh ranks sixth among the high TB burden countries. In 2007 the estimated national TB burden was as follows: annual incidence of all cases – 223 per 100 000 population; incidence of new smear-positive cases – 100 per 100 000; prevalence of all cases – 387 per 100 000 and TB mortality – 45 per 100 000.[5] These rates correspond to 353 000 incident TB cases (all forms), 159 000 new smear-positive cases and 71 000 deaths due to TB.

In the same year, of the 148 617 TB cases (all forms) notified, 104 193 (72%) were new smear-positive cases. The trend in smear-positive TB case detection steadily increased in recent years before levelling off in 2007 (45%, 61%, 71% and 72% in 2004, 2005, 2006 and 2007, respectively). The male–female ratio for new smear-positive cases was 2:1. On a national scale, the treatment success rate in new sputum smear-positive cases registered during 2006 was 92%. This indicates that MDR-TB should not be a major problem in new cases. As expected, the treatment success rate reported among previously treated cases registered in the same year was lower (78% in relapse, lower in other retreatment categories). A TB prevalence survey, combined with an Annual Risk of TB Infection survey through tuberculin skin testing, was conducted in 2008–2009. The results show a prevalence of smear-positive TB of 79.4 per 100 000 (95% CI 47.1–133.8).

The extent of drug-resistant TB in Bangladesh is not known as no national survey has ever been conducted. However, Table 1 shows drug resistance data from limited surveys carried out in recent years.

Table 1. *Multidrug-resistant tuberculosis rates in new and previously treated cases*

Survey	New cases (%)	Retreatment cases (%)

ICDDR,B/Shyamoli CDC 2001–2003 (*n*=647)[6]	3.3	27.3
ICDDR,B/Shyamoli CDC 2004–2005 (*n*=106)[6]	3.0	15.4
Damien Foundation 1995 (*n*=645)[6]	0.7	6.8
Damien Foundation 2001 (*n*=1041)[7]	0.4	3.0
NTP/NIDCH 2005–2006: Category 2 failures (*n*=96)	N/A	88.0

CDC – chest disease clinic; ICDDR,B – International Centre for Diarrhoeal Disease Research, Bangladesh; NIDCH – National Institute for Diseases of the Chest and Hospital; NTP – National Tuberculosis Control Programme.

The surveys in Shyamoli Chest Disease Clinic (CDC) were conducted in collaboration with the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B).[8] These data are not truly representative since the Shyamoli CDC is a referral centre. The surveys conducted by Damien Foundation were mainly in rural areas (Greater Mymensingh area). A study conducted in 2005–2006 by the NTP in collaboration with the National Institute for Diseases of the Chest and Hospital (NIDCH)[9] showed that, of 96 Category 2 failures, 88% had MDR-TB. Of the MDR-TB strains, 43% were resistant to any of the second-line drugs (14% to ofloxacin, 30% to prothionamide and 6% to para-aminosalicylic acid).

The Global Tuberculosis Report (2009) estimated MDR-TB rates of 3.5% and 20.0% among new and previously treated TB cases, respectively, in Bangladesh. Although the rates of MDR-TB in Bangladesh do not appear to be very high, the absolute number may be significant given the high TB burden. An MDR-TB rate among new cases of 1% translates into approximately 3000 cases per year.

1.5 National Tuberculosis Control Programme strategy

Since the adoption of the DOTS strategy in 1993, nationwide coverage has been achieved. Accessibility to diagnostic and/or treatment services has been further improved through the set-up of additional microscopy centres and links with other health-care providers. The NTP Manager is responsible for programme implementation at central level under the guidance of the Director-General of Health Services and immediate supervision of the Director, Mycobacterial Disease Control (MBDC), who is also Line Director, TB-Leprosy. At the subnational level, the NTP is

integrated into the general health services under the Director (Health) at the divisional level; the Civil Surgeon at the district level; and the *upazila* Health and Family Planning Officer (UH&FPO) at the subdistrict level. Their responsibilities include coordination and supervision of NTP services carried out by designated staff.

Political commitment is manifested in the maintenance of human and financial resources and in the collaboration with nongovernmental organizations (NGOs). The NTP's Strategic Plan to Control TB, 2006–2010 and 2011–2016 was in line with the Stop TB Strategy. In more recent years, DOTS has been introduced in health facilities that do not come under the immediate control of the NTP or even the Ministry of Health and Family Welfare. These include medical college hospitals, chest disease hospitals, military hospitals, other government health facilities, large corporate health facilities and private practitioners. Preliminary evaluation of this intersectoral collaboration shows a positive impact on case detection.

Through joint efforts of different stakeholders, the Bangladesh Country Coordination Mechanism succeeded in obtaining grants from the Global Fund to Fight AIDS, Tuberculosis and Malaria. Technical and in-kind support was also provided by WHO and the Global Drug Facility.

New approaches are being developed to address major challenges. The Green Light Committee[10] approved a project for the treatment of 700 MDR-TB patients. A standardized regimen was adopted and enrolment of patients started in August 2008. The collaboration between the national TB and HIV programmes is also a crucial strategic component.

1.6 Laboratory diagnosis of tuberculosis

Sputum smear microscopy is the cornerstone of TB diagnosis, which is integrated in primary health care facilities (*upazila* health complexes). In several *upazila*, diagnostic services are even further decentralized to peripheral laboratories, covering several unions of one *upazila*. The country has a strong laboratory network mainly focusing on detecting AFB through direct microscopy. There are over 1000 microscopy

centres. External Quality Assurance (EQA) is routinely conducted by designated EQA laboratories. There are 40 of these, mainly located in CDCs, covering 99% of the AFB laboratories linked to the NTP.

The National Tuberculosis Reference Laboratory (NTRL) started functioning in June 2007. It completed its first round of proficiency testing with satisfactory results (accuracy of 96% for rifampicin, 93% for isoniazid, 95% for ethambutol and 100% for streptomycin). The second round of proficiency testing showed 100% accuracy for rifampicin, isoniazid and ethambutol and 93% for streptomycin.

The NTRL is performing mycobacterial cultures on Löwenstein-Jensen media. As per current policy, MDR suspects are referred to the NTRL (located in NIDCH) for culture and drug susceptibility testing (DST). The NTRL also performs molecular DST. Another culture laboratory in Shyamoli CDC is mainly used for research purposes in collaboration with ICDDR,B. The Damien Foundation has its own reference laboratory linked to the Supranational Reference Laboratory (SRL) in Antwerp, Belgium, which is capable of performing cultures and DST for first-line drugs, benefiting patients residing in the NGO's designated work area. The first regional reference laboratory was established by the NTP in 2007 in Rajshahi in collaboration with the Damien Foundation. This laboratory performs liquid cultures and DST. The NTP has also established regional reference laboratories at Chittagong and Khulna and has plans to cover all divisions of Bangladesh.

1.7 Treatment outcomes

Figure 1 shows the trends in DOTS coverage, case detection and the treatment success rate of new smear-positive cases (1995–2007), while Table 2 compares the treatment outcome rates for new and relapse smear-positive patients registered in 2007.

Figure 1. ***Trends in DOTS coverage, 1995–2007***

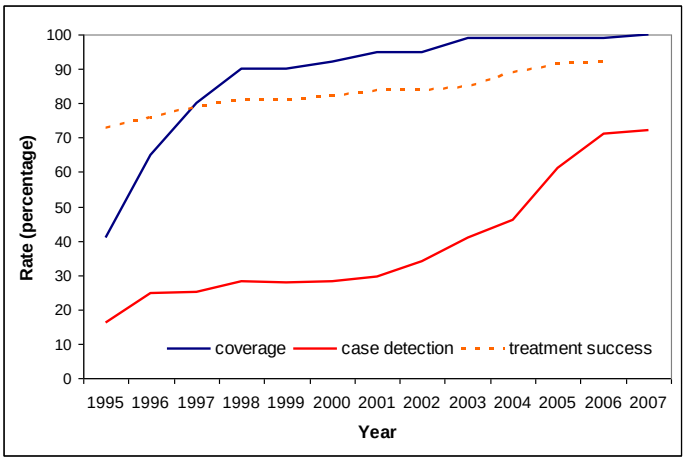


Table 2. *Treatment results for new and relapse smear-positive cases registered in 2007*

Outcome	New (*n*=101 183)	Relapse (*n*=3858)
Cured	91%	71%
Treatment completed	1%	7%
Died	3%	5%
Failure	1%	2%
Defaulted	2%	4%
Transferred out	2%	4%
Not evaluated	0%	8%

Source: National Tuberculosis Control Programme.

1.8 Statements of problem and rationale

Resistance to commonly prescribed TB drugs and especially to isoniazid and rifampicin (MDR-TB) is most often caused by incorrect TB treatment. It is thus a man-made phenomenon. Factors such as irregular drug supply, inappropriate prescription or poor adherence may permit multiplication of drug-resistant strains and, consequently, create resistance. This is called acquired resistance. Subsequent transmission of these resistant strains from an infectious case to other persons may lead

to TB disease characterized by resistance from the onset. This is known as primary resistance. Primary and acquired drug resistance have enormous implications for control programmes as well as for patient therapy.

Acquired drug resistance is a good indicator of current treatment practices in the community while initial drug resistance measures disease transmission in a community and highlights the challenges that a TB control programme will encounter when administering chemotherapy.

Knowledge of anti-TB drug (ATD) resistance levels is an essential public health management tool for evaluating and improving the performance of NTPs. This knowledge is also essential for the management of patients with drug-resistant TB. The few drug resistance studies that have been conducted in Bangladesh describe resistance patterns in selected areas of the country showing, in general, variable levels of drug resistance.

To determine the prevalence of drug resistance countrywide and strengthen the TB drug resistance surveillance system, it is necessary to carry out a nationwide survey. Such a study is useful to evaluate TB control interventions, rationalize standardized regimens for new and retreatment cases, and assist in proper planning of the programme for managing drug-resistant forms of TB.

Bangladesh has completed its first national tuberculosis drug resistance survey. This survey was conducted under the overall guidance of the National Tuberculosis Control Programme (NTP) Bangladesh at the National Tuberculosis Reference Laboratory (NTRL), National Institute of Diseases of the Chest and Hospital, in collaboration with WHO, the Supranational Reference Laboratory (SRL), Antwerp, Belgium, and different NGO partners *(see Acknowledgements, p. vii)*.

The survey is expected to provide information on the prevalence of anti-TB drug resistance among new and previously treated patients and will contribute to a better understanding of the national and international situation of TB drug resistance.

1.9 Goal and objectives of the tuberculosis drug resistance survey

The overall goal was to improve the efficiency of TB control in Bangladesh.

The general objective was to strengthen the detection and monitoring for anti-TB drug resistance among TB patients in Bangladesh. The specific objectives of the drug resistance survey were:

(1) to determine the prevalence and drug resistance patterns of first-line anti-TB drugs among newly diagnosed and previously treated sputum-positive cases;

(2) to determine the prevalence and drug resistance patterns of second-line anti-TB drugs in strains with confirmed resistance to isoniazid and rifampicin;

(3) to speciate mycobacteria isolated from sputum smear-positive cases.

2. Materials and methods

2.1 Study design

The study was cross-sectional, targeting all new and previously treated smear-positive TB patients.

2.2 Sample size determination

In 2009, a total of 109 200 new smear-positive cases were notified countrywide. The proportion of rifampicin resistance among newly diagnosed patients was assumed to be 1.2%. It was expected to measure a difference in proportion of 1% (change of 2%) with a 95% CI. To detect this change a sample size of 454 smear-positive patients was required (obtained using Epi Info 7 StatCalc programme). Since a cluster sampling strategy was employed, the sample size was doubled to 908 to accommodate an estimated design effect of 2. Taking into account the expected losses due to culture contamination and/or patients whose susceptibility testing did not yield interpretable information, the sample size was increased by 20%.

The total sample therefore included 1080 new smear-positive patients. In addition, specimens were collected and tested from previously treated cases registered in the selected cluster, as well as in the CDCs located in the same district as the selected cluster during the period that the new patients were included. CDCs were asked to send previously treated cases throughout the year.

2.3 Sampling strategy

The sampling strategy used in this survey was based on the weighted cluster sampling method in which clusters were selected with probability-proportional-to-size, and in each cluster a fixed number of new patients were included. The primary sampling unit in the survey was the DOTS/diagnostic centre. The cluster sampling method was appropriate in Bangladesh because of the logistic difficulties to cover all

diagnostic centres in the country and the large number of TB cases notified. Within each cluster, a consecutive number of eligible patients were enrolled for the study. Each diagnostic centre represented a cluster. In total, 40 clusters including two subclusters and 34 CDCs/districts were selected. In each cluster, it was planned to enrol a total of 27 new smear-positive patients as well as all retreatment smear-positive cases registered during the same period.

Based on the 2008 and 2009 case notifications, the number of retreatment cases may have been too low to make a conclusion with statistical significance. In order to increase their number, retreatment cases diagnosed in the CDCs located in the same district as the selected cluster were also included.

The following methodology was used to select the clusters. A list of all diagnostic centres in the country with the number of new registered patients for the years 2008 and 2009 was compiled. From this list, a cumulative patient population list was derived. A random number (552) had been picked between zero and the sampling interval. The sampling interval of 5390 equals the number of total smear-positive cases (215 635) divided by the number of clusters (40). This determined the first diagnostic centre to be selected from the cumulative list. The sampling interval was sequentially added to the random number to identify the remaining clusters from the list. From this procedure a total of 40 diagnostic centres were selected for the survey (Annexes 1 and 2).

Taking into account the expected workload for the NTRL and the monitoring capacity of the NTP, the study duration was limited to 12 months. Data from 2008 and 2009 showed that 27 new smear-positive cases could be identified within four months in most clusters. All newly diagnosed smear-positive patients were included in the survey until the required number was reached in each cluster. In order to achieve a balanced workload for the NTRL, five clusters were added every month. This was based on the average monthly notification rate during 2008–2009 and takes into account the additional samples required for pilot-testing. In addition, samples from two retreatment cases per month were added from each CDC. The targeted enrolment rate is shown in

Annex 3. When the survey was at its peak, the NTRL processed almost 500 samples per month.

Patients meeting the inclusion criteria but who were not included in the survey for various reasons were replaced by other patients diagnosed in the same centre according to the sampling procedure described. The selected centres were required to submit sputum specimens of previously treated patients in addition to those of new cases during the time that new cases were included.

Inclusion criteria

- Newly registered sputum smear-positive cases according to WHO/International Union Against Tuberculosis and Lung Disease criteria.
- Children under the age of 15 who satisfy the definition of a positive TB smear, as they may give an indication of recent transmission of drug-resistant strains.
- Previously treated cases (relapse, failure, return after default and chronic cases) presenting to the diagnostic centre or CDC during the intake period.

Exclusion criteria

- Newly registered cases with sputum smear-negative pulmonary TB.
- Patients with extrapulmonary TB.

2.4 Logistics

Transport of samples

Transport of samples was planned twice a week. The target transit time during the survey was a maximum of four days. The transport medium used was 1% cetylpyridinium chloride (CPC) in equal volume of the sputum. Attention was given to logistics in order to minimize the

transport time and to prevent breakage and contamination. The mode of transport was therefore decided on a cluster-by-cluster basis depending on local conditions as observed and discussed during the pre-survey visit. Specimens were transported using disposable carton boxes that held the 50 ml Falcon tubes (wrapped in sealed plastic bags with absorbent padding material, e.g. tissue paper, around the tubes) and could be properly closed and dispatched to the NTRL by courier twice a week. A commercial courier service typically takes one day to deliver the goods. Dispatch notes were signed at both ends to monitor transit times. One cluster and one CDC delivered specimens by hand due to the short distance.

Preparatory and pre-survey visit

One visit was made by the supervisory team (NTP/NTRL/NIDCH/WHO/CDC and NGO partners) to each of the 40 selected clusters and related CDCs prior to the training workshops. This visit was used to explain to the local stakeholders the objectives and methods of the survey; review laboratory conditions (premises, equipment, supplies, procedures); conduct a needs assessment including identification of persons responsible for local data collection and determination of transport of samples; and to anticipate problems in accessibility (e.g. during floods) or any other problem and suggest ways of solving them. The pre-survey visit had been announced well in advance so that it could be undertaken most efficiently. All divisional/district health and administrative authorities were informed about the survey. The checklist used during the pre-survey visit is shown in Annex 4.

Supervisory visit

A supervisory visit was made to check procedures, verify that all eligible patients were included (based on the laboratory or treatment register), monitor completeness and quality of clinical information forms, and to repeat four to six interviews of enrolled patients to verify the quality of the clinical information reported. For these interviews, a random sample was selected of patients who came for DOTS on that day. Data collected during this repeat interview was entered on a separate form (i.e. the

original form was not updated) using the patient's identifier for comparison at the analysis stage. A short standardized monitoring report was produced. To the extent possible, problems identified were addressed on the spot. The standard pre-survey checklist and forms were used in the supervisory visit (Annex 4).

All the rifampicin-resistant TB cases and three non-rifampicin-resistant TB cases per cluster were re-interviewed after receiving the DST result. Additional supervisory visits were made to two clusters.

Human resources

In addition to the recruitment of a research assistant, personnel working in clusters and CDCs were involved because of their microscopy and DOTS training. These were categorized into three groups: (1) administrative head: UH&FPO from the clusters and junior consultants from the respective CDCs; (2) data collectors: medical officer disease control or the medical officer in charge from respective clusters and junior consultants from respective CDCs; and (3) medical technologists: laboratory trained technicians/programme organizer from health-care facilities (from clusters or CDCs) for sample collection, microscopy, sample packing and shipment. One person from group three was designated as the focal person for carrying the drug resistance survey (DRS) kit from the NTRL, keeping it in his/her possession, coordinating with other research assistants, shipping the samples, keeping a copy of all records and dealing with the supervisors' visit from the NTP. A total of 225 research assistants were involved in the field.

The medical officer disease control (preferably) or the medical officer in charge, consultants of the clusters and CDCs, respectively, interviewed the patients and completed the questionnaires; and laboratory technologists/programme organizer provided support to collect and transfer samples. Training over three days was provided by the NTP and NTRL prior to their involvement in the field work.

Data entry and laboratory staff

Two data entry operators were recruited for 12 months to work at the NTRL to collect the data and enter them into the computer, in addition to the 10 NTRL staff who were involved in the survey.

Staff training

Training sessions, held shortly before the start of the survey, were divided into groups of 3–5 clusters per session, including related CDCs. The research assistants recruited for the survey were trained intensively for three days on the use of the questionnaire (Annex 5), inclusion and exclusion criteria, patient classification, history taking, probing into socioeconomic conditions and health-seeking behaviour, specimen collection, handling and shipment.

In addition, all relevant health workers involved in the survey were invited to participate in a one-day orientation meeting in the same sitting at the NTP. These health workers included both government and NGO staff, UH&FPO of the selected cluster, central and divisional supervisors, and district supervisors of the NGOs.

2.5 Laboratory activities

Sputum collection procedures

Patients suspected of having TB were assessed according to routine procedures. The patient produced a sputum sample on the spot, brought an early morning sputum the next day and produced another sample
(3–5 ml) on the spot. If one of these smears was positive, the patient was interviewed by a data collector. If the patient was considered smear-positive according to routine diagnostic criteria, the two highest grade positive sputum samples were transferred to 50 ml Falcon tubes provided by the NTRL and kept at room temperature, containing 5 ml of 1% CPC and 2% sodium chloride in water. The patient's TB serial number in the centre's register as well as a unique patient code were written on the container's label (not on the cover) and protected with

scotch tape. Each cluster or CDC had been given the unique codes for enrolling patients during the training period.

While waiting for delivery to the NTRL, sputum samples in the CPC-containing Falcon tubes continued to be kept at room temperature. At least twice a week, the stored and labelled samples were packed into proper transport boxes or disposable cartons and transported to the NTRL through the courier services designated during the pre-survey visit. The questionnaire (Annex 5), sputum shipment form (Annex 6) and consent form (Annex 8) accompanied the specimens, while duplicate copies were kept at the centre.

Patient enrolment

The first patient enrolled was from the cluster named the National Anti-Tuberculosis Association of Bangladesh, Chittagong on 27 December 2010 and the last patient was listed on 19 November 2011 from Cox's Bazar CDC.

Laboratory procedures

On arrival at the NTRL, the specimens along with their accompanying forms were given laboratory identification numbers (DR-No.) and relevant information was checked and entered in the NTRL laboratory register. EpiInfo was used as the data entry software. All procedures involving the handling of specimens for culture and DST were carried out in a Level 2 biosafety cabinet.

All samples were cultured following standardized procedures. Sputum samples were concentrated by centrifugation at 3000 *x g* and washed with distilled water twice. The concentrated deposit was cultured on two slopes of Löwenstein-Jensen medium with glycerol at 37 °C for up to eight weeks. Culture slopes were inspected after 48 hours to detect contamination and thereafter weekly to observe growth. Sediments were kept at 4 °C for one week or until a first reading excluded contamination; contaminated cultures were replaced by culturing again from the refrigerated sample sediment after a short decontamination procedure.

All positive culture slopes of *M. tuberculosis* were identified by growth rate on Löwenstein-Jensen medium, acid-fastness, colony morphology, pigment production and 500 μg/ml para-nitrobenzoic acid sensitivity. All strains with any characteristic suggestive of mycobacteria other than TB (MOTT) were forwarded to SRL Belgium for further identification.

Drug susceptibility testing

Löwenstein–Jensen media was used for all resistance testing by the proportion method, at the following critical concentrations: 0.2 μg/ml isoniazid, 40 μg/ml rifampicin, 4 μg/ml dihydro-streptomycin sulphate and 2 μg/ml ethambutol. The control medium without drugs was prepared at the same time as the drug-containing media.

After performing susceptibility tests on all the positive cultures, those destined for quality control at SRL Belgium were kept at room temperature. Every two months or earlier, one batch of strains was placed in transport tubes (one loopful of colonies in 2 ml cryovials with a few drops of distilled water) and dispatched to SRL Belgium. In total, 258 strains in 7 batches were sent to SRL for EQA.

All survey strains were kept in a deep freezer at –80 °C as a loopful of colonies in skim milk medium and water for 2–4 years. All testing followed the standard operating procedures at the NTRL, which are based on globally accepted procedures.

Quality assurance measures

Quality assurance was organized to detect system errors and improve compliance with survey procedures. This was applied to all essential elements of the survey including (1) sampling (selection of patients enrolled in the study); (2) clinical information (the distinction between never treated and previously treated); and (3) laboratory techniques used at the peripheral level and at the NTRL. To ensure that DST results were reliable and comparable, internal and external quality control of susceptibility testing were performed during the survey. Any strain showing resistance (including isoniazid and/or rifampicin resistance),

MOTT strains and some pan-susceptible strains among new and retreatment cases, were sent to SRL Belgium on a two-monthly or earlier basis. All rifampicin-resistant strains were also tested at SRL for resistance to second-line drugs (ofloxacin, kanamycin). DNA fingerprinting for 12 selected strains from 2 clusters was also done at SRL.

2.6 Pilot study

The whole process of patient identification, completion of forms, sputum collection, administration and sample shipment was tested in a short pilot phase. This was to identify major logistical problems. Every cluster was asked to perform the study procedures on four consecutive patients suspected for TB. All forms and specimens (regardless of microscopy result) were sent to the NTRL according to protocol. The samples of the first two test patients were sent on a Saturday, the samples of the last two test patients were sent on a Wednesday. At the NTRL, the transit time of the samples and the quality of the submitted documents were monitored by a study team. Adjustments were made in close communication with the submitting centre, if needed. The submitted samples were discarded without being examined.

2.7 Ethical considerations

Ethical clearance of the survey protocol was received from the Bangladesh Medical Research Council.

The patients were given routine care within the NTP. The only difference with other routine practices was the addition of DST on the collected sputum samples. The results were communicated to the DOTS facility, who notified the patient. Patients diagnosed with MDR-TB were treated according to the NTP guidelines for drug-resistant TB.

2.8 Data management and analysis

After receiving the data at the NTRL, all forms were checked for completeness and registers were kept of incoming forms. A staff

member was specifically assigned for this task. Two data entry clerks entered all data. Any discrepancy noted in the data form was resolved by mobile communication with the focal person, as far as possible.

Original copies of data sheets (Annex 7) were sent to the respective diagnostic centre with the culture and DST results. Duplicates were retained at the NTRL for final analysis. All data collected from the survey were double-entered by different persons in a computer. Any discrepancy in the information was resolved by checking the data sheets. The WHO software SDRTB4 was used. Data cleaning, validation and analysis were performed using the SDRTB or other statistical software.

Data was analysed according to a data analysis plan that was written before the final analysis took place. Prevalence of drug resistance was calculated from the number of cases with a DST result available. The number of missing results due to contamination, negative cultures and insufficient growth for DST was also reported.

2.9 Analysis of patient intake

The analysis of patient intake is included in Table 3a of the number of patients from each cluster compared with the target number of patients.

2.10 Analysis of drug resistance patterns

An analysis of drug resistance patterns is included in Table 5 describing the proportion of patients with mono-resistance to each drug and combined resistance to different combinations of drugs among new and previously treated patients. Data are presented based on mutually exclusive categories of resistance, namely mono-resistance and different types of combined resistance. Where necessary, the data are stratified by age, gender, patient type and geographical locality. To estimate current transmission of drug-resistant strains in the population, the prevalence of drug resistance in young age groups was also calculated.

2.11 Survey coordination

At regular intervals (preferably every month) during the intake period, the Principal Investigator presented a progress report (including tabulated data) to the core group of the DRS Steering Committee and quarterly reports to the full DRS Steering Committee. The reports included information on field work, such as enrolment of patients, quality of clinical information collected, transport or logistic problems and contamination of samples. If the data suggested that a significant problem had occurred, the DRS Steering Committee or its core group assisted the Principal Investigator in analysing the situation and developing a plan for remedial action.

2.12 Monitoring and supervision

Pre-survey and ongoing survey monitoring visits were performed before the training and in the middle of the survey by a team formed of the NTP, NTRL, NIDCH, WHO, USAID and NGO partners. Three external technical teams also visited the NTP, NTRL and selected clusters/CDCs for monitoring and validation of the survey.

2.13 Policy implications of survey findings

Data derived from the survey will primarily be used for surveillance purposes and not for individual case management. Consequently, individual patient management shall continue to be based on existing policies established by the NTP. This includes management of patients identified as having MDR-TB.

2.14 Ownership of the data

The data of the survey are owned by the NTP, who retains any decision on dissemination and/or publication of the data.

3. Results

3.1 Inclusion of tuberculosis patients

The duration of the project was 12 months (from December 2010 to November 2011). During this time period a total of 1480 TB patients were interviewed, including both new and retreatment cases. Figure 2 outlines the flow chart of the study, while Figure 3 shows the sampling status, in which 9% of the samples had no DST.

Figure 2. *Flowchart of the study*

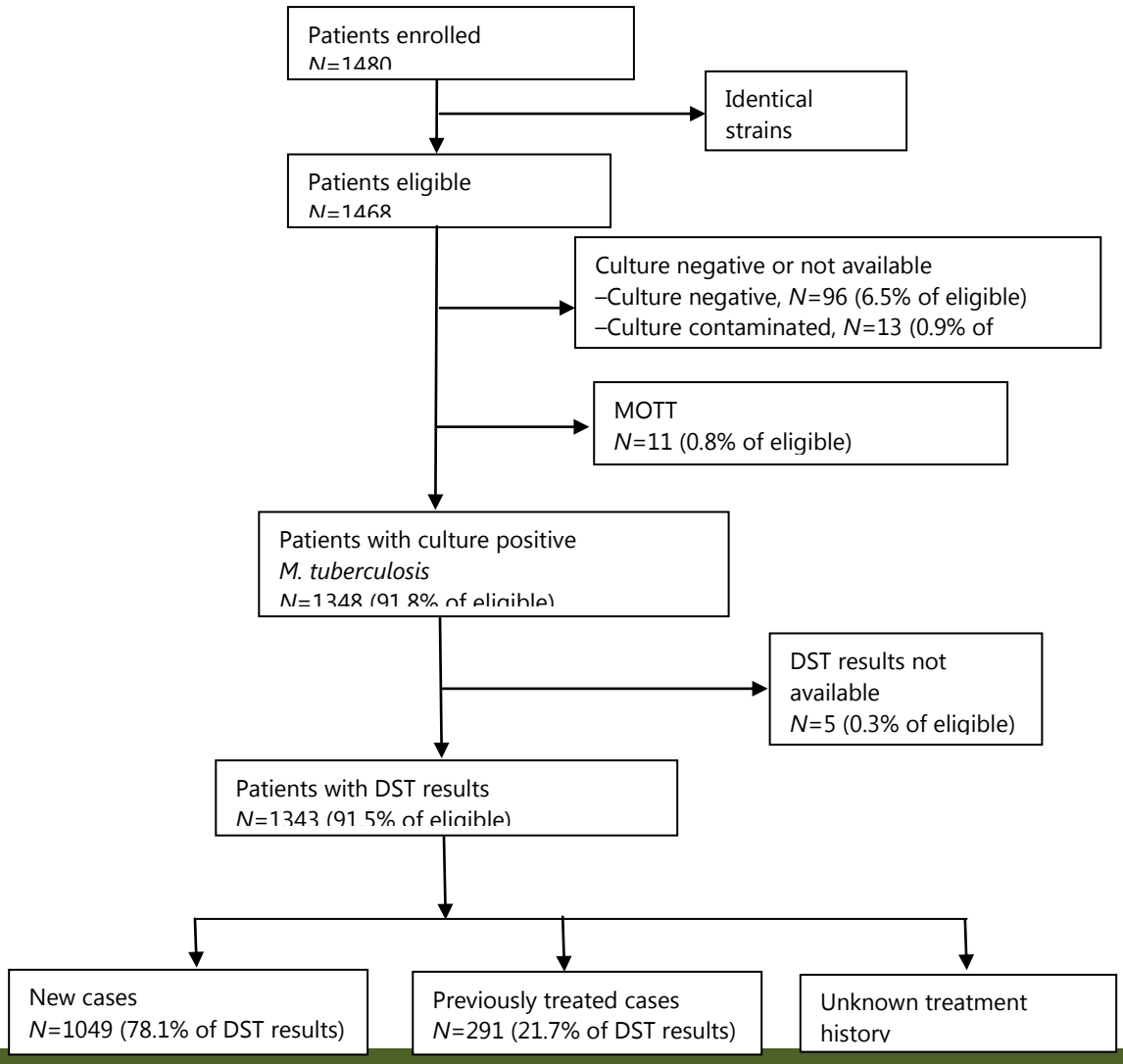
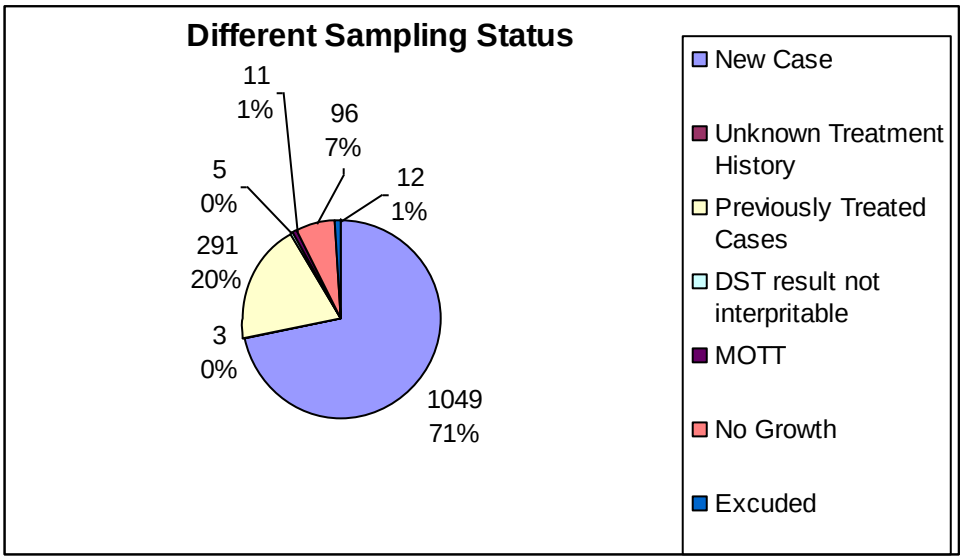


Figure3. ***Sampling status of the study***



Tables 3a to 3d show a breakdown of the patients enrolled. Tables 3a and 3b show the number of new smear-positive TB cases planned and ultimately enrolled, by cluster and district, respectively. Tables 3c and 3d show the enrolment of previously treated cases by cluster and district, respectively.

Table 3a. *Number of new smear-positive tuberculosis study patients, by cluster*

No	Cluster/health-care facility	District	Number of cases planned	Number of cases included	Percentage of cases needed
1	Dhaka Export Processing Zone	Dhaka	27	27	100.0
2	National Anti-Tuberculosis Association of Bangladesh	Chittagong	27	27	100.0
3	Muradpur+RB, Concerned Women for Family Development	Dhaka	27	27	100.0
4	UHC Digholia	Khulna	27	29	107.4
5	UHC Debigonj	Panchagarh	27	28	103.7
6	Aftabnagor+Kaf,	Dhaka	27	29	107.4

No	Cluster/health-care facility	District	Number of cases planned	Number of cases included	Percentage of cases needed
	Population Services and Training Centre				
7	Bangladesh Rural Advancement Committee, Dhakkinkhan	Dhaka	27	30	111.1
8	UHC Baraigram	Nator	27	29	107.4
9	UHC Mohangonj	Netrokona	27	27	100.0
10	UHC Harinakunda	Jhenaida	27	28	103.7
11	UHC Bahubal	Hobigonj	27	29	107.4
12	UHC Fulbari	Dinajpur	27	29	107.4
13	UHC Daolatpur	Manikgonj	27	28	103.7
14	UHC Dewangonj	Jamalpur	27	29	107.4
15	UHC Nazirpur	Pirojpur	27	29	107.4
16	UHC Tongibari	Munsigonj	27	27	100.0
17	UHC Bhurungamari	Kurigram	27	29	107.4
18	UHC Bagharpara	Jessore	27	27	100.0
19	UHC Mirzapur	Tangail	27	28	103.7
20	UHC Monohorgonj	Comilla	27	27	100.0
21	UHC Golapgonj	Sylhet	27	28	103.7
22	UHC Aditmari	Lalmonirhat	27	29	107.4
23	UHC Bondor	Narayangonj	27	28	103.7
24	UHC Palashbari	Gaibandha	27	32	118.5
25	UHC Muladi	Barisal	27	27	100.0
26	UHC Gabtali	Bogra	27	29	107.4
27	Cox's Bazar Sadar	Cox's Bazar	27	27	100.0
28	UHC Kasba	Brahmanbaria	27	29	107.4
29	UHC Ramgonj	Lakshmipur	27	28	103.7
30	UHC Daudkandi	Comilla	27	29	107.4
31	UHC Faridgonj	Chandpur	27	27	100.0

No	Cluster/health-care facility	District	Number of cases planned	Number of cases included	Percentage of cases needed
32	UHC Chhatak	Sunamgonj	27	28	103.7
33	UHC Golachipa	Patuakhali	27	28	103.7
34	UHC Mirshrai	Chittagong	27	27	100.0
35	UHC Sreepur	Gazipur	27	29	107.4
36	UHC Feni Sadar	Feni	27	27	100.0
37	UHC Shahazadpur	Sirajgonj	27	29	107.4
38	Mymensingh Sadar	Mymensingh	27	27	100.0
39	UHC Daulatpur	Khustia	27	29	107.4
40	UHC Savar	Dhaka	27	27	100.0
Total			**1080**	**1127**	**104.4**

UHC: *Upazila* health complex.

Table 3b. *Number of new smear-positive tuberculosis study patients, by district*

No	District	Number of cases planned	Number of cases included	Percentage of cases needed
1.	Brahmanbaria	27	29	107.4
2.	Barisal	27	27	100.0
3.	Bogra	27	29	107.4
4.	Chandpur	27	27	100.0
5.	Chittagong	54	54	100.0
6.	Comilla	54	56	103.7
7.	Cox's Bazar	27	27	100.0
8.	Dhaka	135	140	103.7
9.	Dinajpur	27	29	107.4
10.	Feni	27	27	100.0
11.	Gaibandha	27	32	118.5
12.	Gazipur	27	29	107.4

No	District	Number of cases planned	Number of cases included	Percentage of cases needed
13.	Hobigonj	27	29	107.4
14.	Jamalpur	27	29	107.4
15.	Jessore	27	27	100.0
16.	Jhenaida	27	28	103.7
17.	Khulna	27	29	107.4
18.	Khustia	27	29	107.4
19.	Kurigram	27	29	107.4
20.	Lakshmipur	27	28	103.7
21.	Lalmonirhat	27	29	107.4
22.	Manikgonj	27	28	103.7
23.	Munsigonj	27	27	100.0
24.	Mymensingh	27	27	100.0
25.	Narayangonj	27	28	103.7
26.	Nator	27	29	107.4
27.	Netrokona	27	27	100.0
28.	Panchagarh	27	28	103.7
29.	Patuakhali	27	28	103.7
30.	Pirojpur	27	29	107.4
31.	Sirajgonj	27	29	107.4
32.	Sunamgonj	27	28	103.7
33.	Sylhet	27	28	103.7
34.	Tangail	27	28	103.7
Total		**1080**	**1127**	**104.6**

Table 3c. *Number of previously treated smear-positive tuberculosis study patients, by health-care facility (cluster)*

No	Cluster/health-care facility	District	Number of cases included
1	Export Processing Zone	Dhaka	0
2	National Anti-Tuberculosis Association of Bangladesh	Chittagong	3
3	Muradpur+RB, Concerned Women for Family Development	Dhaka	2
4	UHC Digholia	Khulna	0
5	UHC Debigonj	Panchagarh	0
6	Aftabnagor+Kaf, PSTC	Dhaka	3
7	Bangladesh Advancement Committee, Dhakkinkhan	Dhaka	2
8	UHC Baraigram	Nator	3
9	UHC Mohangonj	Netrokona	2
10	UHC Harinakunda	Jhenaida	1
11	UHC Bahubal	Hobigonj	2
12	UHC Fulbari	Dinajpur	0
13	UHC Daolatpur	Manikgonj	0
14	UHC Dewangonj	Jamalpur	3
15	UHC Nazirpur	Pirojpur	0
16	UHC Tongibari	Munsigonj	1
17	UHC Bhurungamari	Kurigram	0
18	UHC Bagharpara	Jessore	0
19	UHC Mirzapur	Tangail	0
20	UHC Monohorgonj	Comilla	1
21	UHC Golapgonj	Sylhet	3
22	UHC Aditmari	Lalmonirhat	5
23	UHC Bondor	Narayangonj	1
24	UHC Palashbari	Gaibandha	0
25	UHC Muladi	Barisal	1

No	Cluster/health-care facility	District	Number of cases included
26	UHC Gabtali	Bogra	3
27	Cox's Bazar Sadar	Cox's Bazar	0
28	UHC Kasba	Brahmanbaria	1
29	UHC Ramgonj	Lakshmipur	0
30	UHC Daudkandi	Comilla	0
31	UHC Faridgonj	Chandpur	3
32	UHC Chhatak	Sunamgonj	1
33	UHC Golachipa	Patuakhali	1
34	UHC Mirshrai	Chittagong	2
35	UHC Sreepur	Gazipur	2
36	UHC Feni Sadar	Feni	0
37	UHC Shahazadpur	Sirajgonj	1
38	Mymensingh Sadar	Mymensingh	1
39	UHC Daulatpur	Khustia	0
40	UHC Savar	Dhaka	1
Total			**49**

UHC: *Upazila* health complex.

Table 3d. *Number of previously treated smear-positive tuberculosis study patients, by chest disease clinic or health-care facility (cluster)*

No	District	Total number of cases in CHCs and health-care facilities (clusters)
1	Brahmanbaria	17
2	Barisal	13
3	Bogra	6
4	Chandpur	13
5	Chittagong	64
6	Comilla	8
7	Cox's Bazar	9

No	District	Total number of cases in CHCs and health-care facilities (clusters)
8	Dhaka	39
9	Dinajpur	2
10	Feni	3
11	Gaibandha	15
12	Gazipur	2
13	Habiganj	2
14	Jamalpur	16
15	Jessore	10
16	Jhinaidaha	1
17	Khulna	17
18	Kurigram	6
19	Kustia	23
20	Lakshimipur	0
21	Lalmonirhate	5
22	Manikganj	0
23	Munshigonj	4
24	Mymensingh	2
25	Narayangonj	1
26	Nator	24
27	Netrokona	2
28	Panchagargh	0
29	Patuakhali	5
30	Pirjojpur	0
31	Sirajgonj	10
32	Sunamgonj	2
33	Sylhet	19
34	Tangail	13
Total		**353**

3.2 Demographic profiles of eligible patients

Demographic profiles of the eligible TB patients included in the drug resistance survey are shown in Table 4. More than two thirds of the patients were male (70.8%), and 75.6% of all patients had a monthly income level less than 7500 Taka (US$ 97). The majority of the enrolled patients (85.9%) lived in non-metropolitan areas and a quarter (25%) were farmers.

Table 4. *Characteristics of eligible patients*

	New cases		Previously treated cases		Unknown history of treat.		Total cases		P value
	n	%	n	%	n	%	n	%	
Total	1,124	100.0	341	100.0	3	100.0	1,468	100.0	
Sex									0.030
- Male	778	69.2	259	76.0	3	100.0	1,040	70.8	
- Female	346	30.8	82	24.1	0	0.0	428	29.2	
Age group, years									0.252
- 0-14	12	1.1	5	1.5	0	0.0	17	1.2	
- 15-24	238	21.2	52	15.3	0	0.0	290	19.8	
- 25-34	258	23.0	80	23.5	0	0.0	338	23.0	
- 35-44	165	14.7	69	20.2	1	33.3	235	16.0	
- 45-54	164	14.6	49	14.4	0	0.0	213	14.5	
- 55-64	142	12.6	51	15.0	1	33.3	194	13.2	
- ≥65	142	12.6	34	10.0	1	33.3	177	12.1	
- Unknown	3	0.3	1	0.3	0	0.0	4	0.3	
Place of residence									0.000
- Non-metropolitan area	1,031	91.7	227	66.6	3	100.0	1,261	85.9	
- Metropolitan area	93	8.3	114	33.4	0	0.0	207	14.1	
Occupation									0.000
- Farmer	304	27.1	64	18.8	2	66.7	370	25.2	
- Businessman	95	8.5	34	10.0	0	0.0	129	8.8	
- Daily labourer	114	10.1	40	11.7	0	0.0	154	10.5	
- Driver	41	3.7	25	7.3	0	0.0	66	4.5	
- Garment worker	84	7.5	13	3.8	0	0.0	97	6.6	
- Housewife	225	20.0	54	15.8	0	0.0	279	19.0	
- Retired	15	1.3	14	4.1	1	33.3	30	2.0	
- Student	43	3.8	16	4.7	0	0.0	59	4.0	
- Service holder	59	5.3	27	7.9	0	0.0	86	5.9	
- Unemployed	69	6.1	23	6.7	0	0.0	92	6.3	
- Other	73	6.5	28	8.2	0	0.0	101	6.9	
- Unknown	2	0.2	3	0.9	0	0.0	5	0.3	
Division									0.000
- Barisal	81	7.2	17	5.0	0	0.0	98	6.7	
- Chittagong	249	22.2	106	31.1	0	0.0	355	24.2	
- Dhaka	362	32.2	78	22.9	1	33.3	441	30.0	
- Khulna	113	10.1	51	15.0	0	0.0	164	11.2	
- Rajshahi	87	7.7	38	11.1	2	66.7	127	8.7	
- Rangpur	147	13.1	28	8.2	0	0.0	175	11.9	
- Sylhet	85	7.6	23	6.7	0	0.0	108	7.4	
Income (Taka)									0.045
- ≤2,500	128	11.4	30	8.8	0	0.0	158	10.8	
- 2,500<5,000	372	33.1	78	22.9	2	66.7	452	30.8	
- 5,000<7,500	364	32.4	134	39.3	1	33.3	499	34.0	
- 7,500<10,000	64	5.7	18	5.3	0	0.0	82	5.6	
- 10,000<15,000	108	9.6	43	12.6	0	0.0	151	10.3	
- 15,000<20,000	13	1.2	9	2.6	0	0.0	22	1.5	
- ≥20,000	21	1.9	9	2.6	0	0.0	30	2.0	
- Unknown	54	4.8	20	5.9	0	0.0	74	5.0	
HIV status									0.858
- Negative	1	0.1	0	0.0	0	0.0	1	0.1	
- Positive	0	0.0	0	0.0	0	0.0	0	0.0	
- Unknown	1,123	99.9	341	100.0	3	100.0	1,467	99.9	

3.3 Patients tested and loss

Among 1480 patients, 12 identical strains were identified, leaving 1468 eligible patients. Of these, 96 (6.5%) had negative cultures, 13 (0.9%) had contaminated cultures, 11 (0.8%) were infected with MOTT. Among the remaining 1348 (91.8%) patients with positive cultures, 5 (0.3%) did not have readable DST results, leaving a total of 1343 (91.5%) patients with valid DST results. The majority of these enrolled patients – 1049 (78.1%) – were new smear-positive cases of TB and the remaining 291 (21.7%) were previously treated cases (Figures 1 and 2).

3.4 External quality assurance of the drug susceptibility test results

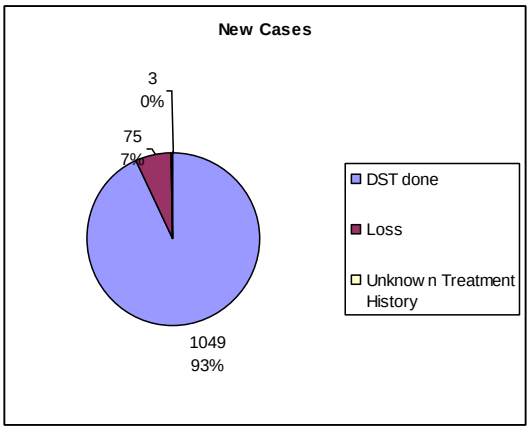
A total of 258 isolates from 1480 TB patients were selected for rechecking, 5 of which failed to grow from subculture and 4 were contaminated. Therefore, the DST results of 249 isolates tested at the NTRL were retested by SRL Belgium. Eleven MOTT confirmations and DNA fingerprinting of 12 selected strains were also carried out at SRL.

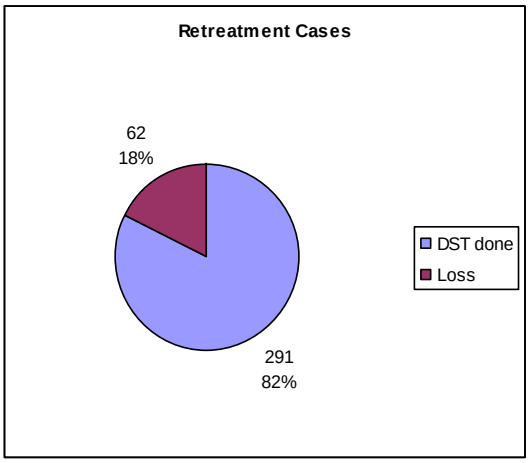
A few retests were clearly different to the NTRL results, and the latter were therefore replaced by the second results obtained at SRL. However, the overall accuracy was 97% for isoniazid and 94% for rifampicin. These results were highly appreciated by SRL in their report, considering the high workload caused by such a survey.

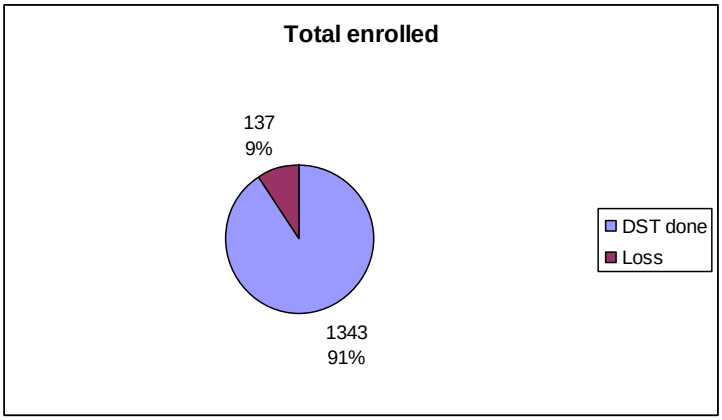
As per protocol, second-line (ofloxacin, kanamycin) DST was performed in SRL Belgium for selected MDR strains only.

MOTT were only found in 11 species, which were identified by molecular methods (16S ribosomal ribonucleic acid (rRNA) technique). There were also two mixtures of TB with MOTT, which were not further specified and not evaluated for DST results.

Figure 4. ***Percentage loss of new and retreatment cases***







3.5 Drug resistance results

New cases

A total of 1049 new TB cases were tested (Table 5). Of these, about 88% were infected with pan-susceptible strains (95% CI 84.0–90.7). Prevalence of MDR-TB among new cases was 1.4% (95% CI 0.7–2.5%) and total mono-resistance in new cases was 8.4% (95% CI 5.9–11.9). However, mono-resistance to rifampicin and isoniazid was 0.2% and 1.4%, respectively, and the total poly-resistance was 2.5% (95% CI 1.6–3.9).

Previously treated cases

A total of 291 previously treated TB cases were tested (Table 5). Of these, 56.8% were infected with pan-susceptible strains (95% CI 50.5–62.9%). Prevalence of MDR-TB among previously treated cases was 28.5% (95% CI 23.5–34.1). Total mono-resistance in previously treated cases was 10% (95% CI 7.3–13.5). However, mono-resistance to rifampicin and isoniazid was 0.4% and 2.5%, respectively, and the total poly-resistance was 4.7% (95% CI 2.6–8.5).

Table 5. *Pattern of resistance to first-line anti-TB drugs (weighted)*

Drug-resistance pattern	No. (% [95% CI]) New (n 1,049)	Previously treated (n 291)	Total (n 1,343)
Susceptible to all drugs	87.7 (84.0–90.7)	56.8 (50.5–62.9)	81.3 (77.3–84.8)
Any drug resistance			
- Any resistance to H	5.3 (3.9–7.0)	35.8 (29.9–42.0)	11.6 (9.0–14.8)
- Any resistance to R	1.6 (0.9–2.9)	28.9 (23.9–34.4)	7.3 (5.2–10.1)
- Any resistance to E	0.9 (0.4–2.1)	17.8 (13.5–23.3)	4.4 (3.2–6.0)
- Any resistance to S	9.9 (7.4–13.0)	33.1 (27.1–40.0)	14.7 (11.9–18.0)
Total any drug resistance	12.3 (9.3–16.1)	43.2 (37.1–49.5)	18.7 (15.2–22.7)
Mono drug resistance			
- Mono resistance to H	1.4 (0.8–2.6)	2.5 (1.2–5.2)	1.6 (1.0–2.6)
- Mono resistance to R	0.2 (0.0–1.0)	0.4 (0.0–2.7)	0.3 (0.0–1.1)
- Mono resistance to E	0.2 (0.0–0.8)	0.0 (-)	0.2 (0.0–0.6)
- Mono resistance to S	6.6 (4.4–9.8)	7.1 (4.8–10.3)	6.7 (4.8–9.3)
Total mono drug resistance	8.4 (5.9–11.9)	10.0 (7.3–13.5)	8.7 (6.6–11.5)
Multi drug resistance			
- HR	0.4 (0.1–1.2)	4.3 (2.2–8.2)	1.2 (0.6–2.4)
- HRE	0.0 (0.0–0.7)	3.0 (1.8–5.0)	0.7 (0.4–1.3)
- HRS	0.4 (0.2–1.1)	7.0 (5.1–10.0)	1.8 (1.1–2.8)
- HRES	0.5 (0.2–1.3)	14.1 (9.9–19.7)	3.3 (2.3–4.9)
Total multi drug resistance	**1.4 (0.7–2.5)**	**28.5 (23.5–34.1)**	**7.0 (5.0–9.8)**
Polydrug resistance			
- HE	0.1 (0.0–0.8)	0.0 (-)	0.0 (0.0–0.6)
- HS	2.4 (1.5–3.7)	4.0 (2.2–7.2)	2.7 (1.9–3.9)
- ES	0.0 (-)	0.0 (-)	0.0 (-)
- HES	0.0 (-)	0.7 (0.2–2.9)	0.2 (0.0–0.6)
- RE	0.0 (-)	0.0 (-)	0.0 (-)
- RS	0.0 (-)	0.0 (-)	0.0 (-)
- RES	0.0 (-)	0.0 (-)	0.0 (-)
Total polydrug resistance	2.5 (1.6–3.9)	4.7 (2.6–8.5)	3.0 (2.1–4.2)

E: ethambutol; H: isoniazid; R: rifampicin; S: streptomycin; Z: pyrazinamide.

Tables 6a–d show the proportions of MDR in previously treated cases in different subcategories.

Table 6a: *Proportions of MDR in previously treated cases (8 subcategories)*

	Relapses of CAT I % (95% CI) (n tested)	Relapses of CAT II % (95% CI) (n tested)	Failures of CAT I % (95% CI) (n tested)	Failures of CAT II % (95% CI) (n tested)	Defaulters of CAT I % (95% CI) (n tested)	Defaulters of CAT II % (95% CI) (n tested)	Other % (95% CI) (n tested)	Unknown % (95% CI) (n tested)	All previously treated % (95% CI) (n tested)
MDR	13.3 (8.0-21.4) (157)	56.8 (38.1-73.8) (34)	49.0 (26.1-72.4) (27)	75.8 (53.9-89.3) (28)	13.5 (3.6-39.7) (25)	14.8 (1.7-63.0) (7)	40.8 (7.3-85.8) (11)	0.0 - (3)	28.5 (23.5-34.1) (291)

Table 6b: *Proportions of MDR in previously treated cases (5 subcategories)*

	Relapses % (95% CI) (n tested)	Failures % (95% CI) (n tested)	Defaulters % (95% CI) (n tested)	Other % (95% CI) (n tested)	Unknown % (95% CI) (n tested)	All previously treated % (95% CI) (n tested)
MDR	21.1 (14.8-29.1) (191)	63.2 (47.0-76.9) (55)	13.8 (5.0-32.9) (32)	40.8 (7.3-85.8) (11)	0.0 - (3)	28.5 (23.5-34.1) (291)

Table 6c

	Tested	% MDR	Univariate			
			OR	95%CLs		p value
Previously treated						
- Relapses of CAT I	157	13.3	REF			
- Relapses of CAT II	34	56.8	8.6	3.5	21.2	0.000
- Failures of CAT I	27	49.0	6.3	2.3	16.7	0.001
- Failures of CAT II	28	75.8	20.3	6.8	61.0	0.000
- Defaulters of CAT I	25	13.5	1.0	0.3	4.0	0.981
- Defaulters of CAT II	7	14.8	1.1	0.2	6.0	0.886
- Other	11	40.8	4.5	0.9	22.2	0.065
- Unknown	3	0.0	1.0	-	-	-

Table 6d

	Tested	% MDR	Univariate			
			OR	95%CLs		p value
Previously treated						
- Relapses	191	21.1	REF			
- Failures	55	63.2	6.4	3.1	13.3	0.000
- Defaulters	32	13.8	0.6	0.2	2.0	0.392
- Other	11	40.8	2.6	0.5	13.2	0.246
- Unknown	3	0.0	1.0	-	-	-

CAT: category; n: number; OR: odds ratio; REF: .

Notes on Tables 6a–d

Relapses of CAT I: when TB patients get well after taking isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) combination, but revert to being TB positive patients.

Relapses of CAT II: when TB patients get well after taking isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin (HRZES) combination, but revert to being TB positive patients.

Failures of CAT I: when TB patients continue taking HRZE, but do not get well and still show TB positive results up to 5 months later.

Failures of CAT II: when TB patients continue taking HRZES, but do not get well and still show TB positive results up to 5 months later.

Defaulters of CAT I: TB patients took HRZE for more than one month but did not show up for next two months and came back again as TB positive cases.

Defaulters of CAT II: TB patients took HRZES for more than one month but did not show up for next two months and came back again as TB positive cases.

A pattern of resistance to second-line drugs among MDR-TB cases (weighted) was also examined in this study (Table 6). It was found that among new cases there was no resistance for ofloxacin, kanamycin or XDR-TB. Among previously treated cases, resistance was found for ofloxacin.

Table 7. *Patterns of resistance to second-line drugs among MDR-TB cases (weighted)*

Resistance	New 15 % (95% CI) (n tested)	Previously treated 84 % (95% CI) (n tested)	All 99 % (95% CI) (n tested)
ofloxacin	0 (-) (14)	23.8 (13.0-39.7) (60)	19.2 (11.3-30.5) (74)
kanamycin	0 (-) (14)	0 (-) (60)	0 (-) (74)
XDR	0 (-) (14)	0 (-) (60)	0 (-) (74)

3.6 Analysis of risk factors for drug resistance

All variables recorded (sex, age, history of TB treatment, and place of residence) were included in the univariate analysis and in the multivariate analysis if p >0.05. As expected, a history of previous anti-TB treatment was the strongest independent factor for any drug resistance (OR 29, 95% CI 15.9–53.0) and MDR-TB (OR 34.9, 95% CI 18.5–65.8). In addition, the univariate analysis showed that living in metropolitan areas increased the risk of any drug resistance (OR 2.5, 95%CI 1.4–4.6) and MDR-TB (OR 0.7, 95% CI 0.4–1.2), respectively (Table 7). From logistic regression analysis, it was found that other factors such as age, sex, occupation, income, etc. had no effect on drug resistance of TB patients, except in the age group below 45 years, which showed a significantly high rate of MDR-TB. Missing values were imputed using different modelling scenarios, although the results did not differ significantly from those obtained without imputation indicating that missing values did not play a role in determining levels of drug resistance in the survey.

Table 8. *Risk factors for MDR-TB*

	Tested	% MDR	Univariate				Multivariate			
			OR	95%CLs		p value	OR	95%CLs		p value
Sex										
- male	948	6.9	REF							
- female	395	7.2	1.0	0.6	1.9	0.87				
Age group, years										
- 0-24	290	9.8	REF							
- 25-34	318	5.9	0.6	0.4	0.9	0.024	0.4	0.2	0.8	0.012
- 35-44	216	6.4	0.6	0.3	1.4	0.252	0.3	0.1	0.8	0.018
- 45-54	189	7.9	0.8	0.4	1.6	0.517	0.7	0.3	1.4	0.258
- 55-64	174	6.6	0.6	0.3	1.2	0.168	0.4	0.2	0.8	0.015
- ≥65	152	4.7	0.5	0.2	1.1	0.073	0.5	0.2	1.4	0.178
- Unknown	4	0.0	1.0	-	-	-	1.0	-	-	-
History of treatment										
- New cases	1,049	1.4	REF				REF			
- Previously treated cases	291	28.5	29.0	15.9	53.0	0	34.9	18.5	65.8	0.000
- Unknown	3	0.0	1.0	-	-	-	1.0	-	-	-
Place of residence							REF			
- Non-metropolitan area	1,159	5.6	REF							
- Metropolitan area	184	13.8	2.5	1.4	4.6	0.003	0.7	0.4	1.2	0.193
Occupation										
- Farmer	336	6.0	REF							
- Businessman	116	9.3	1.6	0.6	4.2	0.311				
- Daily labourer	140	5.8	1.0	0.4	2.1	0.922				
- Driver	63	8.8	1.5	0.6	3.9	0.376				
- Garment worker	94	2.2	0.4	0.1	1.9	0.217				
- Housewife	254	8.1	1.4	0.7	2.6	0.296				
- Retired	25	4.3	0.7	0.1	6.7	0.755				
- Student	53	12.4	2.2	0.9	5.5	0.084				
- Service holder	80	5.1	0.8	0.3	2.4	0.750				
- Unemployed	87	11.6	2.1	0.6	7.2	0.246				
- Other	91	4.4	0.7	0.3	2.1	0.544				
- Unknown	4	25.5	5.4	0.5	59.6	0.165				
Division										
- Barisal	89	7.5	REF							
- Chittagong	323	9.0	1.2	0.4	4.2	0.735				
- Dhaka	399	4.0	0.5	0.2	1.6	0.243				
- Khulna	150	11.9	1.7	0.5	5.5	0.372				
- Rajshahi	113	10.2	1.4	0.5	3.7	0.476				
- Rangpur	164	3.5	0.5	0.1	1.8	0.255				
- Sylhet	105	6.7	0.9	0.1	5.4	0.905				
Income (Taka)										
- ≤2,500	143	7.4	REF							
- 2,500<5,000	411	5.2	0.7	0.4	1.2	0.176				
- 5,000<7,500	457	7.3	1.0	0.5	1.8	0.962				
- 7,500<10,000	80	5.2	0.7	0.2	2.7	0.572				
- 10,000<15,000	141	11.1	1.6	0.8	3.0	0.192				
- 15,000<20,000	19	5.4	0.7	0.1	6.5	0.757				
- ≥20,000	27	9.0	1.2	0.4	4.3	0.733				
- Unknown	65	8.6	1.2	0.5	2.7	0.711				
HIV status										
- Negative	1	0.0	REF							
- Positive	0	-	-	-	-	-				
- Unknown	1,342	7.0	1.0	-	-	-				

CAT: category; CI: confidence interval; MDR: multidrug resistant; n: number; OR: odds ratio; REF: tuberculosis

4. Discussion

4.1 Organization of the survey

This was the first time that the NTP completed a national TB drug resistance survey. It was completed within two years of establishing the NTRL, which was the key point for conducting the survey.

The drug resistance survey was essential to analyse the effectiveness of the TB control programme as well as to identify the spread of TB-resistant strains in young adults. It was also necessary for Bangladesh in planning to address drug-resistant TB, mainly MDR-TB, which was included in the Stop TB Strategy in 2008. In this study, 40 clusters and 26 CDCs in 34 districts were selected. No single organization was selected; rather it was a multisectoral project with a focus on transparency. Collaborations among stakeholders were enthusiastic and personnel working in the clusters/ *upazila* health complexes and CDCs were selected as research assistants because of their training in DOTs. This also enabled the NTP to perform similar studies in the future. The NTP has a good laboratory network covering 100% of geographical areas, and so there were no difficulties in selecting research assistants; rather it was more cost-effective. The three days of training were found to be beneficial, although displacement of Government of Bangladesh employees hampered data collection in a few places.

Targets of enrolment were achieved in due time except in two clusters: in one cluster, CPC tubes were crystallized due to low temperature; in another cluster, consecutive patients were not enrolled and therefore, they were asked to repeat the process again. This was probably due to non-adherence to DRS training by the senior medical technologist. In another two clusters, 12 strains (9+3) were suspected to be identical and finally confirmed by SRL by MIRU-VNTR analysis. The supply chain was excellent and no shortage was reported. Locally made transport boxes were used and shipment by courier was effective. There was no delay and no loss of specimens. Three technical assistance visits from abroad and survey visits from internal resources found no major errors, and validated the process during their briefing sessions.

Challenges of management of MDR-TB need further resource mobilization. WHO has estimated that over 500 000 cases of MDR-TB occur annually with 150 000 deaths. There are no national data for MDR-TB, although due to the high TB prevalence (sixth among high TB burden countries), WHO ranks Bangladesh ninth among 27 high MDR burden countries.[4]

4.2 Patient enrolment

In this study a total of 1480 new and previously treated patients were enrolled, from which DST results from 1343 (91.5%) were found to be eligible (Figure 2). Among them, 1049 (78.1%) and 291 (21.7%) patients were new and previously treated TB cases, respectively. Three patients failed to give actual drug history and 11 patients were in other groups and did not fall in the designated categories in the questionnaire.

In this regard, category-wise notification of previously treated TB cases from each district may be implemented. In the protocol, the sample loss was estimated to be 20%; however, in reality it was found to be only 9.3 %, which includes no growth (6.5%), culture contamination (0.9%), MOTT (0.8%) and non-interpretable DST results (0.3%). This indicates that the laboratory performance was satisfactory, as endorsed by SRL. Twelve identical strains from two clusters (9+3, 0.8%) needed more field-level monitoring of the DOTS programme by the NTP supervisory team. The CPC transport system was found to be effective.

4.3 Sociodemographic characteristics of the study population

Table 4 shows the sociodemographic characteristics of the enrolled population. It reveals that 70.8% of all TB patients were male and 75.8% had income levels less than 7500 Taka, (US$ 97) proving that TB is a disease of the poor. The majority of patients enrolled (85.9%) were from non-metropolitan areas, which was proportionate to smear-positive TB cases in 2008 and 2009.[9,10] The major occupation of TB patients was farming (25.2%) followed by housewives (19.0%). About three quarters of patients were below the age of 55 years, a finding that correlates

with other investigations and indicates that TB is affecting the main contributors of GDP.[12] HIV status of patients was not included in the survey as it is still of low prevalence in Bangladesh.[11] Health-seeking behaviour and smoking status were also not analysed as these have no effect on drug resistance.

4.4 Prevalence of drug resistance

Table 3 shows the resistance phenotype of first-line anti-TB drugs. The prevalence of MDR-TB among new and previously treated cases was 1.4% (CI 0.7–2.5%) and 28.52% (CI 23.5–34.1), respectively. Mono-resistance to rifampicin and isoniazid (0.2% and 0.4%, 1.4% and 2.5%, respectively), and poly-resistance (2.6% and 4.7%, respectively) were also low in these two groups.

Table 4 shows that 23.8% of the 60 MDR strains were ofloxacin-resistant in previously treated cases. There was no XDR strain. These findings are in accordance with other studies. This fluoroquinolone is being included in the WHO approved Category 4 regimen, which may need to be replaced by another member in the near future. In Indonesia, a similar study found that the levels of drug resistance detected in Central Java Province were relatively low and likely to be due to a well performing TB control programme.[11] According to WHO,[12] anti-TB drug resistance is a major public health problem that threatens progress made in TB care and control worldwide. Drug resistance arises due to improper use of antibiotics in chemotherapy of drug-susceptible TB patients.

This improper use is a result of a number of actions, including administration of improper treatment regimens and failure to ensure that patients complete the whole course of treatment. Essentially, drug resistance arises in areas with weak TB control programmes. A patient who develops active disease with a drug-resistant TB strain can transmit this form of TB to other individuals.

Table 9. *Comparative drug resistance survey data of main parameters of selected countries*

Country	MDR Rate (new cases in 2006)	MDR rate (previously treated cases in 2006)	Mono-resistance in new cases		Mono-resistance in previously treated cases	
			RIF	INH	RIF	INH
India (Gujarat State)	2.8%	17.2%	2.5%	11.0%	18.1%	36.8%
Myanmar	3.9%	15.5%	4.6%	6.5%	15.5%	26.7%
Viet Nam	2.7%	19.3%	3.3%	19.1%	21.3%	43.5%
Thailand	1.7%	34.5%	2.6%	9.7%	35.1%	44.3%
Indonesia	2.0%	18.9%	2.0%	12.9%	Data available only for new cases	
Latvia	10.8%	36.3%	10.8%	30.9%	36.3%	49.5%
Peru	5.3%	23.6%	5.8%	11.6%	26.4%	30.3%
South Africa	1.8%	6.7%	2.1%	5.9%	7.9%	11.8%
Bangladesh (2010–2011) current study	1.4%	28.5%	0.2%	1.4%	0.4%	2.5%

INH: isoniazid; RIF: rifampicin

The data of this survey largely correspond with other countries of the WHO South-East Asia Region but differ with other countries. High prevalence of MDR-TB in new cases in other countries (Table 6) may be due to high prevalence of HIV infection, inappropriate regimens or poor quality anti-TB drugs.[13] The above findings appear as indicators of:

(a) good laboratory performance of the DRS as mentioned in the SRL report;

(b) an effective TB control programme;

(c) an appropriate regimen and the good quality of the anti-TB drugs used;

(d) a limited spread of drug resistant and MDR-TB among the community.

High mono-resistance to streptomycin may be due to cross-reactivity with other drugs, its indiscriminate use against other diseases and its easy availability in the pharmacy.[14] Low mono-resistance to rifampicin and isoniazid indicates that these critical anti-TB drugs were introduced timely in the programme and there was no monotherapy with these drugs.

The first global data concerning resistance to anti-TB drugs, obtained by the WHO and the International Union against Tuberculosis and Lung Disease, were published in their 1997 report, and matched the results of the resistance surveillance carried out in monitoring laboratories from 35 different countries around the globe from 1994 to 1997.[15] Evidence of primary multi-resistance found in all 35 countries was subject to study. The primary resistance rate median was 1.4%, although it reached 14.4% in Latvia and rose over 2% in one out of three countries. It came as no surprise that countries with insufficient anti-TB programmes were the most affected by MDR. Global resistance figures provided by the report clearly depicted the full extent of this health-care issue in some areas. In Latvia, 30% of patients under anti-TB treatment were infected by multiresistant strains; in the Russian Federation this figure reached 5%, 10% in the Dominican Republic and 13% in India (New Delhi).[9] Subsequent surveillance reports dating from 2000, 2004, 2008 and 2010 increased the number of countries studied to 109. The findings indicated that resistance rates remained stable in countries with low TB incidence, but became dramatically high in Eastern Europe including Azerbaijan, the Baltic republics, Kazakhstan, Republic of Moldova, the Russian Federation, Uzbekistan, and others such as the Republic of Korea, Peru and some Chinese and Indian provinces.

Official WHO data regarding multi-resistance[12] estimate between 390 000 and 510 000 new cases of MDR-TB worldwide for 2008. This figure corresponds to 3.6% of all cases (95% CI 3.0–4.4).

4.5 Risk factors of multidrug-resistant tuberculosis

A large body of literature describes risk factors associated with default from first-line TB therapy. These include patient-related factors, such as

alcoholism, drug use, treatment-related adverse events, prior treatment default, lack of social support, and low socioeconomic status,[16-19] and programmatic risk factors such as poor patient–provider, communication and barriers to accessing care.[20] This study shows that patients in non-metropolitan areas are less likely to have drug resistance. However, this is not a very strong finding and should be pursued further in the future health survey and in the routine drug-resistant TB surveillance planned by the NTP. Like the present study, Moniruzzaman et al[21] found no relationship between educational status, gender and drug resistance. On the other hand, a previous study reported that 56.7% of MDR-TB cases occurred among those with poor economic status.[22] Sen et al[23] determined that low socioeconomic status made the risk of MDR 7.02 times higher. Low socioeconomic status was also considered to be an obstacle to appropriate and necessary treatment once the initial diagnosis was made. Further study on the effectiveness of the NTP is needed.

In this study, the risk of MDR-TB is more or less equal among both sexes (p=0.87) but higher in patients aged below 45 years (p=0.024) or more than 65 years (p=0.073). This finding is also absent in other studies.[11] This is probably due to both men and women being equally exposed to resistant strains due to their occupation or health-seeking behaviour. Older patients exposed previously to sensitive strains developed acquired resistance during anti-TB treatment. However, younger patients have developed resistance to strains more recently due to their occupation or health-seeking behaviour. The prevalence of MDR-TB in metropolitan areas was significantly higher (p=0.003) than in non-metropolitan areas. This may be due to non-compliance of the patients, non-adherence of the private sector to the DOTS programme and/or poor quality of anti-TB drugs sold in the pharmacy.

There was no significant higher risk of MDR-TB in relation to occupation, location or income of the patient (p>0.5). The main risk factor for MDR-TB is the history of previous anti-TB therapy. Table 3 shows that the treatment failure group had a significantly higher rate of MDR-TB (p<0.05). This finding correlates with other studies.[24,25]

The NTP Bangladesh seems to have a good TB control programme. It adopted the Green Light Committee-approved Programmatic Management of Drug-Resistant TB (PMDT) programme launched at NIDCH in 2008, and gradually expanded the treatment facilities of drug-resistant TB. A research-oriented nine-month regimen exists in the drug facility area of the country.

The NTP also adopted the community-based PMDT programme funded by TB CARE-II. Laboratory expansion is also under way in each division, including molecular DST up to district level for early diagnosis and treatment of drug-resistant TB. Though the rate of MDR-TB among new cases is low, there will be in total about 4000 cases per year due to the high prevalence of the disease. Early intervention is necessary to prevent emergence of primary MDR-TB.

5. Limitations of the study

All of the participating health service centres were DOTS centres and/or CDCs. Therefore, patients from the private sector were not included in the study. However, it is assumed that all retreatment cases were referred to CDCs and were thus ultimately enrolled. Other limitations were that:

- data on health-seeking behaviour were not analysed;
- displacement of trained research assistants from the clusters/CDCs may have disrupted data collection during the survey;
- only solid culture and DST were performed in the study;
- HIV status of the enrolled patients was not determined;
- the number of retreatment cases was fewer than expected.

6. Conclusions and recommendations

6.1 Conclusions

The NTP Bangladesh has completed its first DRS survey, 41 years after the Liberation War, and within a few years of establishment of the NTRL. Government commitment was of the highest level to complete the survey. Government and NGO collaboration was found more useful than involving a single organization for such a nationwide study, and allowed transparency for every stakeholder.

The prevalence of MDR-TB in new and previously treated cases was 1.4% and 28.5%, respectively. Drug history, residence and age of the patients were found to be significantly related with MDR prevalence. In this study, culture loss was lower than estimated (8.2% instead of 20%).

The TB control programme was found to be effective. Data validate the study and predict a well-run programme. Supply management through WHO was excellent and of high quality.

6.2 Recommendations

- As this was a baseline survey, it should be repeated every five years to monitor changes in anti-TB drug resistance patterns in the country.
- In a future study, the HIV status of TB patients in the country should also be included.
- Early intervention is necessary in metropolitan areas and should cover the private sector to provide a good quality DOTS programme.
- Replacement of floxacin by another fluoroquinoloneis an important issue in the drug-resistant TB regimen of WHO in Bangladesh.

- Category-wise case notification of previously treated smear-positive TB cases from each district should be implemented.
- Molecular epidemiology (deletion analysis and spoligotyping) can also be analysed from the same strain to see the propagation of primary or acquired resistance in the community.

Although the prevalence of MDR is low, the actual number of MDR cases will be high considering the high prevalence of TB, which ultimately places the country in the 27 high MDR burden countries. The national TB programme thus needs to expand its drug-resistant TB management programme by modifying its operation plan and enhancing further resource mobilization.

In addition, sentinel drug resistance surveillance supports PMDT services, and thus the expansion of sentinel surveillance should be aligned with the expansion of PMDT services. The expansion of quality assured laboratories for DST should follow both the expansion of PMDT services and sentinel drug resistance surveillance.

A survey for drug resistance in extra-pulmonary TB might also be performed.

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Annex 1

Sampling of diagnostic centres

The clusters were selected based on the list of diagnostic centres (40) with the number of new smear-positive cases registered during 2008 and 2009 (total 215 635). The sampling interval was 5390 and the random number chosen was 552. The individual cluster number was allocated after sorting the 40 selected clusters in order of case notification, the cluster notifying the fewest cases receiving number 1 and the cluster with the highest notification receiving number 40.

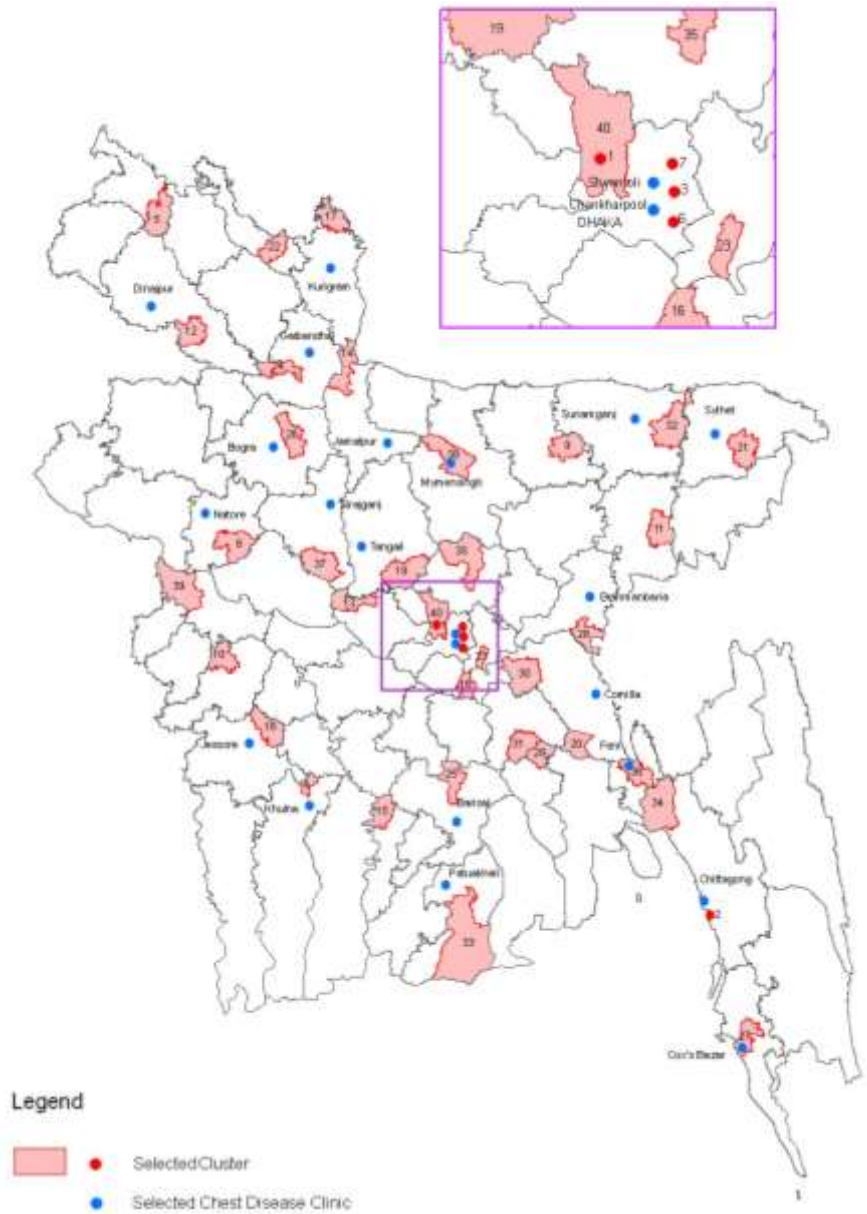
Serial No.	Cluster No.	Division	District	*Upazila*	Average no. of smear-positive cases per year (2008–2009	Cumulative cases
01	05	Rajshahi	Panchagarh	Debiganj	130	771
02	12	Rajshahi	Dinajpur	Fulbari	162	6168
03	22	Rajshahi	Lalmonirhat	Aditmari	219	11 402
04	17	Rajshahi	Kurigram	Bhurungamari	184	17 004
05	24	Rajshahi	Gaibandha	Palasbari	224	22 338
06	26	Rajshahi	Bogra	Gabtoli	230	27 823
07	08	Rajshahi	Natore	Baraigram	149	32 867
08	37	Rajshahi	Sirajganj	Shahazadpur	424	38 854
09	39	Khulna	Kushtia	Daulatpur	475	44 167
10	10	Khulna	Jhenaidah	Harinakunda	153	49 074
11	18	Khulna	Jessore	Bagerpara	201	54 759
12	04	Khulna	Khulna	Digholia	122	59 925
13	15	Barisal	Pirojpur	Nazirpur	176	65 246
14	25	Barisal	Barisal	Muladi	225	70 883
15	33	Barisal	Patuakhali	Galachipa	357	76 586
16	09	Dhaka	Netrakona	Mohanganj	152	81 576

Serial No.	Cluster No.	Division	District	*Upazila*	Average no. of smear-positive cases per year (2008–2009	Cumulative cases
17	38	Dhaka	Mymensingh	Mymensingh Sadar	472	87 115
18	14	Dhaka	Jamalpur	Dewanganj	172	92 451
19	19	Dhaka	Tangail	Mirzapur	201	97 612
20	13	Dhaka	Manikganj	Daulatpur	168	103 258
21	40	Dhaka	Dhaka	Savar	653	109 529
22	35	Dhaka	Gazipur	Sreepur	415	113 792
23	23	Dhaka	Narayanganj	Bandar	220	119 223
24	16	Dhaka	Munshiganj	Tongibari	178	124 637
25	32	Sylhet	Sunamganj	Chattak	350	130 380
26	21	Sylhet	Sylhet	Golapganj	208	135 461
27	11	Sylhet	Habiganj	Bahubal	155	140 761
28	28	Chittagong	Brahmanbaria	Kashba	298	146 522
29	30	Chittagong	Comilla	Daudkandi	310	152 031
30	31	Chittagong	Chandpur	Faridganj	347	156 882
31	29	Chittagong	Lakshmipur	Ramganj	299	162 332
32	36	Chittagong	Feni	Feni Sadar	413	167 898
33	34	Chittagong	Chittagong	Mirsharai	368	173 675
34	27	Chittagong	Cox's Bazar	Cox's Bazar Sadar	277	178 578
35	01	Dhaka	Savar	DEPZ	75	183 858
36	20	Chittagong	Comilla	Monoharganj	205	189 633
37	03	Dhaka	Dhaka City Corporation	CWFD	100	194 678
38	06	Dhaka	Dhaka City Corporation	PSTC	139	200 063
39	07	Dhaka	Dhaka	Dakkhin Khan	141	204 475

Serial No.	Cluster No.	Division	District	*Upazila*	Average no. of smear-positive cases per year (2008–2009	Cumulative cases
40	02	Chittagong	Chittagong City Corporation	NATAB	75	210 966

Annex 2

Map of Bangladesh indicating selected clusters and chest disease clinics



Annex 3

Monthly enrolment target

Cluster no.	Cluster name	Average no. of patients notified per month (2008–2009)	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
1	DEPZ	6		6	6	6	6	6	4			
2	NATAB-Chittagong	6		6	6	6	6	6	4			
	Chittagong CDC			2	2	2	2	2	2	2	2	2
3	CWFD-Dhaka	8		8	8	8	8	7				
	Shyamoli CDC			2	2	2	2	2	2	2	2	2
4	Digholia	10		10	10	10	4					
	Khulna CDC			2	2	2	2	2	2	2	2	2
5	Debiganj	11		11	11	13						
6	PSTC Dhaka	12			12	12	14					
	Chankharpool				2	2	2	2	2	2	2	2
7	Dakkhin Khan	12			12	12	10					
8	Baraigram	12			12	12	10					
	Natore CDC				2	2	2	2	2	2	2	2
9	Mohanganj	13			13	13	8					
10	Harinakunda	13			13	13	8					
11	Bahubal	13				13	13	8				
12	Fulbari	14				14	14	6				
	Dinajpur CDC					2	2	2	2	2	2	2
13	Daulatpur	14				14	14	6				
14	Dewanganj	14				14	14	6				

Cluster no.	Cluster name	Average no. of patients notified per month (2008–2009)	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
	Jamalpur CDC					2	2	2	2	2	2	2
15	Nazirpur	15				15	15	4				
16	Tongibari	15					15	15	4			
17	Burungamari	15					15	15	4			
	Kurigram CDC						2	2	2	2	2	2
18	Bagerpara	17					17	17				
	Jessore CDC						2	2	2	2	2	2
19	Mirzapur	17					17	17				
	Tangail CDC						2	2	2	2	2	2
20	Monoharganj	17					17	17				
21	Golapganj	17						17	17			
	Sylhet CDC							2	2	2	2	2
22	Aditmari	18						18	16			
23	Bandar	18						18	16			
24	Palasbari	19						19	15			
	Gaibandha CDC							2	2	2	2	2
25	Muladi	19						19	15			
	Barisal CDC							2	2	2	2	2
26	Gabtoli	19							19	15		
	Bogra CDC								2	2	2	2
27	Cox's Bazar	23							23	11		
	Cox's Bazar CDC								2	2	2	2
28	Kashba	25							25	9		

Cluster no.	Cluster name	Average no. of patients notified per month (2008–2009)	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
	Brahmanbaria CDC								2	2	2	2
29	Ramganj	25							25	9		
30	Daudkandi	26							26	8		
	Comilla CDC								2	2	2	2
31	Faridganj	29								29	5	
32	Chatak	29								29	5	
	Sunamganj CDC									2	2	2
33	Galachipa	30								30	4	
	Patuakhali CDC									2	2	2
34	Mirsharai	31								31		
35	Sreepur	35								31		
36	Feni	34									31	
	Feni CDC										2	2
37	Shahazadpur	35									31	
	Sirajganj CDC										2	2
38	Mymensingh Sadar	39									31	
	Mymensingh CDC										2	2
39	Daulatpur	40									31	
40	Savar	54									31	
Total patients per month			0	47	113	189	245	247	247	240	213	44
Total samples per month			**0**	**94**	**226**	**378**	**490**	**494**	**494**	**480**	**426**	**88**

Annex 4

Checklist for pre-survey visit to cluster

Name of supervisor: .....

Name of health facility: .....

Cluster number: .....

Date of visit (DD/MM/YYYY): ...../...../2010

Name of Medical Officer in charge of the unit: .....

1. EXPLAIN OBJECTIVES OF THE SURVEY

- ✓ **Overall goal:** To improve efficiency of tuberculosis control in Bangladesh
- ✓ **General objective:** To strengthen detection and monitoring of levels for anti-tuberculosis drug resistance among TB patients in Bangladesh.

Specific objectives:

- ✓ To determine the prevalence and pattern of primary (initial) drug resistance to first-line anti-TB drugs among newly diagnosed sputum-positive cases in the country;
- ✓ To determine the prevalence and drug resistance patterns of first-line anti-TB drugs among previously treated cases;
- ✓ To determine the prevalence and drug resistance patterns to second-line anti-TB drugs in strains with confirmed resistance to isoniazid and rifampicin;
- ✓ To speciate mycobacteria isolated from sputum smear-positive cases; and

- ✓ To determine underlying factors that may contribute to resistance, including socioeconomic situation, treatment compliance, co-morbidity, etc.).

2. ASSESS THE LABORATORY SITUATION (Use laboratory check list)

……

……

……

3. LIST PERSONS IDENTIFIED FOR DATA COLLECTION

Designation	Name	Mobile phone no.	Signature
Laboratory staff			
Clinical officer			
DOTS nurse			
NGO focal point			

4. IDENTIFY MEANS OF SHIPPING SPECIMENS TO NTRL

Name of courier identified: ……..

How much does it cost per parcel? Taka ……

Is there any written contract with the identified courier? ☐ Yes ☐ No

Is there any alternative possibility to ship the specimens to NTRL?

☐ No ☐ Yes: ……

Supervisor: Signature: Date: ……/……/2010

Name: ……

Annex 5

Clinical information form

Name of country: **Bangladesh** Country code: **BAN**

Name of diagnostic centre:.....Centre code:.....

A: PATIENT IDENTIFICATION INFORMATION

Name: .....

TB registration number: .....

Specimen ID:

Smear Result: sample 1 ..... sample 2 .....sample 3 .....

Sex: ☐ Male ☐ Female

Age [whole years]: .....

Residence: ☐ Metropolitan area ☐ Non metropolitan area

B: MEDICAL HISTORY

B 1: Previously treated for TB ?. ☐ No → *Go to B2*

☐ Yes → *Go to B3*

B 2: Standardized history

For how long have you been sick?.....

Did you have the same symptoms prior to this episode? ☐ No ☐ Yes

Did you have other symptoms of lung disease prior to

this episode (haemoptysis, chest pain, cough)? ☐ No ☐ Yes

Did you have X-ray examinations prior to this episode? ☐ No ☐ Yes

Did you have sputum examination prior to this episode?	☐ No	☐ Yes

Did you ever take anti-tuberculosis drugs for more than one month?

☐ No ☐ Yes

If yes, what was the name of the drug(s)? .....

Did you ever have injections for more than a month? ☐ No ☐ Yes

Did the patient remember previous treatment for TB after these questions? ☐ No ☐ Yes

If yes →*Go to B3*

B 3: Information about previous treatment

Where was the patient treated?

☐ Public sector ☐ Private sector ☐ Other. Please specify.....

When was the patient treated?.....

How many times was the patient treated? .....

Which drugs were used for treatment? .....

By whom was the patient treated?.....

What was the outcome of the last treatment according to the patient?

☐ Cured ☐ Not cured ☐ Unknown

C: MEDICAL RECORDS

After extensive checking through the medical record files and the other documents available in the health centre, have you discovered that the patient has been registered for tuberculosis treatment before?

☐ No ☐ Yes

If yes, what was the outcome of the last course of treatment?

☐ Cured ☐ Treatment completed ☐ Defaulted ☐ Failure ☐ Transfer out

D: FINAL DECISION

D1: Patient has been previously treated for tuberculosis for more than one month

☐ Yes (answer to question B1 or B2 and/or C was "Yes")

☐ No (answer to question B1 or B2 and/or C was "No")

☐ Doubtful

D2: If you ticked "Yes" under D1, **what was the outcome of the previous treatment?**

☐ Cured / treatment completed

☐ Failed

☐ Defaulted

☐ Chronic

☐ Relapse/ defaulter not distinguishable

☐ Unknown

ADDITIONAL QUESTIONS

A: SOCIO-ECONOMIC STATUS

1. Occupation during last three months: .....

2. Number of family members: .....

3. Monthly income: from salary: .....from other sources: .....

B. HEALTH SEEKING BEHAVIOUR

1. When you first felt sick:

a. For how long did you wait before seeking health care?.....

b. Did you buy medicine from pharmacy? ☐ Yes ☐ No

c. Did you seek advice from a traditional doctor or private doctor? ☐ Yes ☐ No

d. Did you go to the upazila health complex? ☐ Yes ☐ No

C. SMOKING

1. Do you smoke? ☐ Yes ☐ No If yes, since how many years: .....

Responsible Medical Officer..... Date ...../...../ .....

Annex 6

Sputum shipment form

Name of country: **Bangladesh** Country code: **BAN**

Name of diagnostic centre:..... Centre code:.....

ID no.of the specimen: .....

TB registration number: .....

SPUTUM SAMPLE

Date of sputum collection: ...../...../20.....

Result of smear: ☐ 3+

☐ 2+

☐ 1+

☐scanty (.....AFB/100 hpf)

☐ Negative

Specimen 1 (DD/MM/YYYY): ...../...../20.....

Annex 7

Request and reporting form for TB culture and drug susceptibility test

Patient identification (ID):

TB register number:___Previous TB register number:____ MDR register number:___

Surname and first name of patient:_____

Age (yrs):_____ Sex:____

Ward / Department: _____

Address: _____

*HIV-status: Pos / Neg / Unknown _____

TB Disease type and treatment history

Site: ☐ pulmonary History: ☐ new (never treated before for ≥1 month)

☐ extrapulmonary (specify):_____ ☐ relapse ☐ failure

Previous treatment: ☐Cat.1 ☐ return after default

☐ Cat.2 ☐ chronic excretor

☐ Cat.4 (second-line drugs)☐ MDR contact

☐ Other _____☐ uncertain

Origin of request:

Region ID:_____District ID:_____Local laboratory ID:_____

Date specimen was collected: ____/____/20___Specimen ID number:_____

Local laboratory: smear result: 1st ____ 2nd ____ 3rd ____ specimen

microscopy technique used: ☐ hot Ziehl-Neelsen ☐ direct smear

☐ cold staining ☐ concentrated smear

☐ fluorescence

Request for testing at the reference laboratory:

Reason: ☐ diagnosis Specimen: ☐ sputum

☐ follow-up at …. months during treatment ☐ sputum in preservative, type ……

☐ follow-up at …. months after treatment ☐ other specify):_____

Requested tests: ☐ microscopy (type _____) ☐ culture ☐ DST (first/second line)

Person requesting examination:

Name:_____ Position:_____

* Information that can be disclosed optionally ID = identification number or code

---

Reference laboratory results:

Date received in the Reference Laboratory _____/_____/20_____

Reference Laboratory specimen ID:___

Microscopic examination: previously reported on date _____/_____/20_____

ID #	Neg	1-9	1+	2+	3+

☐ hot Ziehl-Neelsen ☐ cold staining ☐ fluorescence

☐ direct smear ☐ concentrated smear

Culture result: previously reported on date _____/_____/20_____ ☐ will follow

ID #	Contaminated	Neg	Non-TB mycobacteria (species)	*Mycobacterium tuberculosis* complex			
				1–9 colonies actual count	10–100 col 1+	>101–200 col 2+	>200 col 3+

Results of *M. tuberculosis* drug susceptibility testing: ☐ will follow

☐ phenotypic method used _____

☐ genetic method used _____

ID # _____ Legend: S=susceptible; R=resistant; C=contaminated; ND=not done

	INH	Rifampicin	Ethambutol	Streptomycin	Pyrazinamide	Ofloxacin	Kanamycin
µg/ml							
result							

Date: _____/_____/20_____ Signature:_____

Annex 8

Consent form

BANGLADESH FIRST NATIONAL TB DRUG RESISTANCE SURVEY (2010-11)
NATIONAL TUBERCULOSIS PROGRAM (NTP)
DGHS, MOH& FW, Bangladesh

PRINCIPAL INVESTIGATOR: DR SM MOSTAFA KAMAL, ASSISTANT PROFESSOR & COORDINATOR, NTRL, NIDCH, MOHAKHALI, DHAKA

পরীক্ষার জন্য সম্মতি পত্র

আমি নিজের ইচ্ছায় এ সার্ভেতে অংশগ্রহণ করছি যার নাম "Bangladesh First National TB Drug Resistance Survey". আমাকে এ সার্ভে সম্পর্কে বিস্তারিত তথ্যাদি বলা হয়েছে।

আমি নিজের ইচ্ছায় যক্ষা পরীক্ষা করানোর জন্য রাজি আছি।

আমি কফ্ পরীক্ষার করার পরে যক্ষা জীবানু সনাক্ত হলে, পরীক্ষার ফলাফল বুঝিয়ে বলা হবে এবং উপযুক্ত চিকিৎসার ব্যবস্থা করা হবে । সেই সাথে ভবিষ্যতে নিজেকে এবং অন্যকে কিভাবে যক্ষা-এর জীবানু দ্বারা আক্রান্ত হওয়া থেকে রক্ষা করা যায় সেই বিষয়ে আলোচনা করা হবে।

যক্ষা পরীক্ষার জন্য কফ্ নেয়ার আগে আমার সবধরনের প্রশ্ন করার সুযোগ ছিল এবং সমস্ত প্রশ্নের উত্তরও আমাকে যথাযথভাবে দেয়া হয়েছে।

সবকিছু বিবেচনা করে, আমি সেচ্ছায়, স্বজ্ঞানে কোন রকম প্রলোভিত / প্ররোচিত না হয়ে এ সার্ভেতে অংশগ্রহণ করার জন্য সম্মতি দিচ্ছি।

ক্লায়েন্টের স্বাক্ষর বা টিপ সই	কর্তৃপক্ষের স্বাক্ষর	তারিখ

অপ্রাপ্ত বয়স্ক ও বুদ্ধি প্রতিবন্ধীদের জন্য ঃ -

আমি,_____ এই শিশু/কিশোর/কিশোরী/ ব্যক্তির অভিভাবক/নিকট আত্মীয় । যক্ষা পরীক্ষা করানোর জন্য এই শিশু/কিশোর/কিশোরীর/ব্যক্তির কফ্ নেয়ার জন্য আমি পূর্ণ সম্মতি দিচ্ছি।

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Dr Manjur Alam	Uttara, Dakkhinkhan	BRAC	TO	DC and administrative assistance
Jelenkova Nilu	Uttara, Dakkhinkhan	BRAC	Trainer	Sample collection and transportation
Mahmoda Begum	Uttara, Dakkhinkhan	BRAC	PO	Sample collection and transportation

DC: data collector; GOB: Government of Bangladesh; Jr: junior; Lab Tech: laboratory technician; MO: medical officer; PSTC: Population Services and Training Centre; RDRD: Rangur Dinajpur Rural Service