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PRESENT SCENARIO OF DRUG ADHERENCE ON TUBERCULOSIS MEDICINES IN BANGLADESHI PATIENTS: A COMPREHENSIVE REVIEW

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ABSTRACT

Tuberculosis (TB) is a major contributor to the global burden of disease and has received considerable attention in recent years, particularly in developing countries where it is closely associated with HIV/AIDS. Poor adherence to treatment is common despite various interventions aimed at improving treatment completion. Lack of a comprehensive and holistic understanding of barriers to and facilitators of, treatment adherence is currently a major obstacle to finding effective solutions. The aim of this systematic review of qualitative studies was to understand the factors considered important by patients, caregivers and health care providers in contributing to TB medication adherence.

KEYWORDS: Drug Adherence, Tuberculosis Medicine, TB Patients, Bangladesh.

INTRODUCTION

The People's Republic of Bangladesh had a landmass of 144,000 square kilometers and was bordered by India, Burma (Myanmar), and the Indian Ocean. Most of the country was located on the deltas of the Ganges, Jamuna, and the Meghna Rivers. The country was extremely low lying and flat; very little land was elevated more than 10 feet above sea level. During the seasonal monsoons approximately a third of the country flooded. The GDP of Bangladesh in 2007 was growing at a rate of 6% annually. Agriculture was the major industry, engaging approximately 63% of the labor force and accounting for 20% of the total GDP. The cultivation of rice accounted for almost 80% of all land used for agriculture and 97% of total

grain production.3 Most of Bangladesh's food production was used to support its population. Bangladesh had an unemployment rate of 5% (defined as no hours of formal or informal work per week), and underemployment rate of 42% (defined as those in the labor force working fewer than 35 hours a week). In 2007 Bangladesh had six main administrative divisions divided into a total of 64 zilla (districts) that were further divided into 460 upazilas (sub districts). Each upazila had a population of approximately 270,000. All division and district headquarters and most upazila headquarters were located in urban areas under the upazila level; there were 4,451 rural, micro area unions and about 80,000 villages. There were about 240,000 kilometers of roadways in Bangladesh, of which over 90% were unpaved many of which became impassable during the rainy season. In addition, there were about 8,400 kilometers of waterways, though 3,000 kilometers disappeared during the dry season. There were between two and seven motor vehicles per 1,000 population, 5 and approximately 40% of the rural population lived within 2 kilometers of a road that was passable throughout the year.[1]

Tuberculosis is a major public health problem in Bangladesh. The country position was 6th on the list of 22 highest burden TB countries in the world. It is estimated that 300,000 new cases crop up each year, of which about half of them are infectious TB. It is further estimated that about 70,000 people die every year.

Hence, each hour eight persons die of the disease for which very effective treatment (DOT), free of cost, is available in Bangladesh. Before 1993 TB control was limited to TB clinics and TB hospitals. Field implementation of TB control integrated into the general health services, delivered by Upazila Health Complexes (UHC's), started back in 80s. However, NTP Bangladesh revised its strategies and adopted DOTS in 1993. NGO's have been involved since 1994.[2,3]

TB remains a major public health problem in Bangladesh. The country ranks sixth among 22 highest burden TB countries in the world. It is estimated that about 70,000 people die every year due to TB. In 2009, 160,735 TB cases were notified to Nation Tuberculosis Control Program (NTP). Case notification rate of all forms of TB is low at 47%. Although there is no estimate on the prevalence of childhood TB, it is believed that childhood TB is severely under-diagnosed. MDR TB is an emerging threat in Bangladesh. According to WHO estimates, MDR-TB rate among all newly diagnosed cases is estimated at 2.2%, and among previously treated cases at 15%.[5] TB spreading in Bangladesh are shown in figure-1.

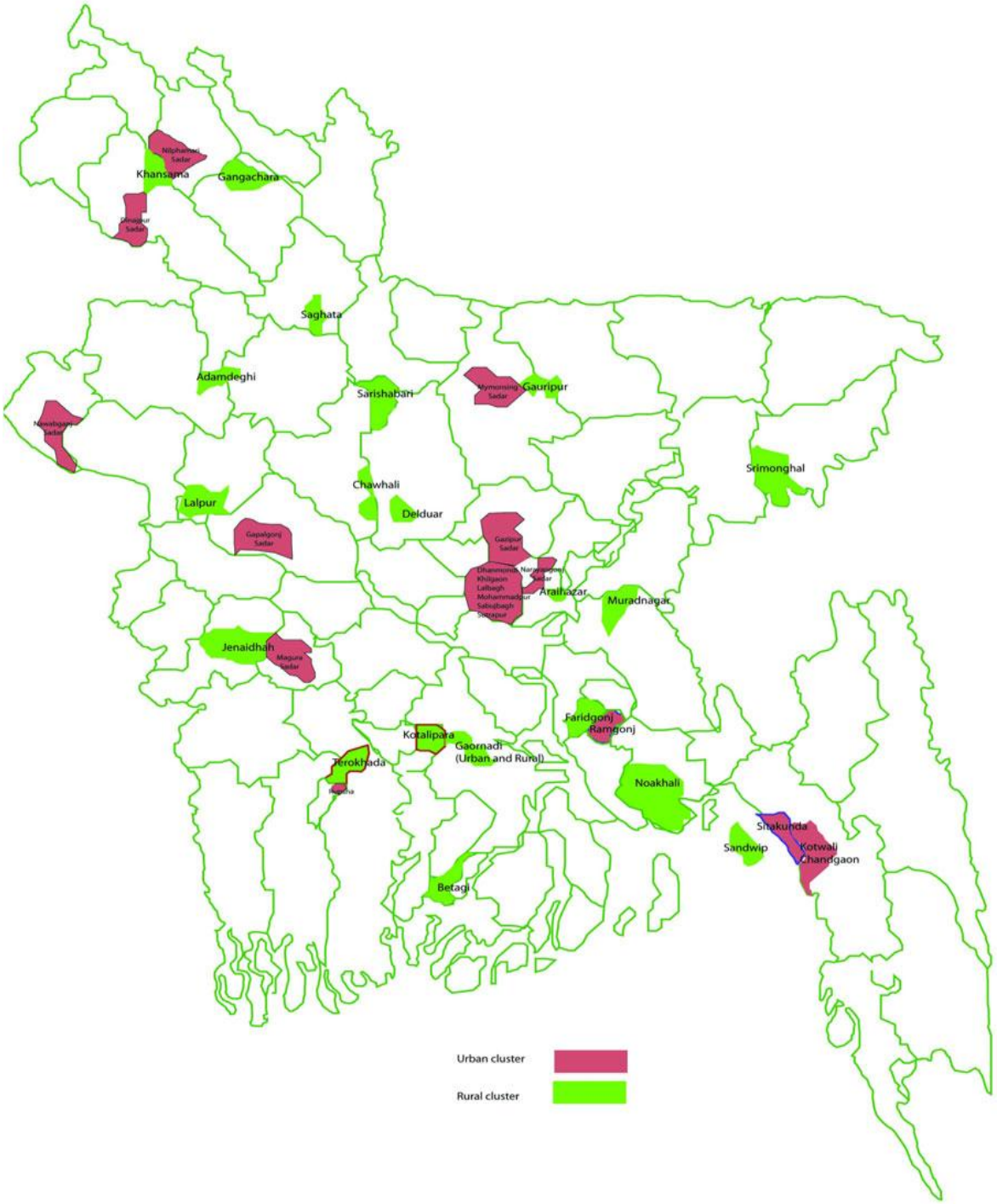

Figure-1: TB spreading in Bangladesh.

FACTORS OF DRUG ADHERENCE

Medication related factors

Studies have found that patients are more convenient on once daily regimens rather than to take their medicines multiple times a day. The number of medicines that the person takes has a negative impact on adherence. This is a big problem especially for older patients who often take more than four medicines for multiple illnesses.

Patient related factors

i. Perception about the nature and severity of the illness. Patients with a disease that requires short term treatment (acute illness) such as malaria or diarrhea adhere better than those who require long term treatment (chronic illness) such as asthma, diabetes, or high blood pressure.

ii. Denial of the illness and the need to take medicines. In Africa, patients who suffer from terminal illnesses such as cancer have often resorted to traditional healers, neglecting conventional medicines.

iii. Assumption that once symptoms improve he or she can discontinue medication. This is a common occurrence in malaria patients who often feel better after the first dose of medicine as the high fever quickly subsides.

iv. Limited appreciation about the value of using medicines properly. People who receive medicines without adequate explanation about how to use them are more like to non-adhere.

v. For example, people who should take a medicine 4 x daily may just take it all at once if they dont ‘understand why the doses need to be spread out.

vi. Acceptance of taking medicines for preventive purposes or for symptomless conditions. Patients who suffer from chronic conditions such as diabetes or cardiovascular disease may be less likely to adhere to treatment once the symptoms are gone.

vii. Worries of social stigma when taking certain medicines. With treatment illiteracy, significant stigma and a variety of misunderstandings about the epidemic of HIV in sub-Saharan Africa, non- adherence is a risk for many people on treatment.

viii. Fear of side effects. This fear may affect adherence for various people, such as women on family planning pills, and people on ARVs. Many people do not know that side effects may be short-lived, manageable and often not as intense as feared.

ix. Fear of needles and the need for self injections. Some people with diabetes who are on insulin require multiple injections and may feel they cannot manage.

x. Media influence regarding safety or risk issues associated with particular medicines. For example in Africa, therapeutically equivalent generic medicines manufactured in Asia are often perceived by the media to be inferior compared to those manufactured in US and Europe.[4, 5]

Prescriber related factors

i. In most national and regional referral hospitals where doctors often have to see large

numbers of patients every day, there is inadequate time to explain to patients the treatment, dosing and side effects. This may lead to poor adherence because the patient may not understand how to take their medicines properly.

ii. In Sub-Saharan Africa, especially rural areas, the medical profession has been infiltrated by quacks masquerading as doctors, pharmacists and other health workers. These people have been prescribing inappropriately, and people have lost trust in the process of getting medical attention.

iii. There is poor communication between prescribers, pharmacists and patients. This may lead to medication errors and poor adherence.[4]

Pharmacy related factors

i. Attitude of patients and pharmacists. Because of the technical nature of the profession, pharmacists have historically taken to simply telling patients what to do, expecting the patient to simply follow instructions. This has not been an effective attitude; most patients faced with such instructions often left the pharmacy without an opportunity to ask questions or clarify instructions, again contributing to poor adherence.

ii. The operational aspect of pharmacy practice. Pharmacy education in most of the Sub-Saharan.

African countries have tended to concentrate on community pharmacy as opposed to pharmacists in thebroader health care delivery system. This has led to many pharmacists operating independently of otherclinical professions, depriving them of (a) important professional / patient interactions and (b) involvementin treatment decisions and care plans.[4]

Government related barriers

i. Regulation on medicine promotion (advertisement). Most medicines' regulatory agencies do not have a robust regulatory framework to combat unethical medicines promotion. This leads to patients receiving biased information directly from the pharmaceutical industry instead of objective, independent information which can help them understand and better adhere to their treatment.

ii. Frequent stock-outs of key essential medicines in public health facilities in the region have caused the public to lose confidence in government health facilities. Patients are often forced to go to private pharmacies and clinics which may be run by people who do not have the time (or make the effort) to interact with patients about their medicines. This

may contribute to non-adherence by patients.

iii. Human resource related factors such as underpaid, overstretched and demoralized health workers are another impediment to effective interactions with patients.[4]

Other factors of patient adherence

There are many factors which can influence the level of patient adherence in any given treatment.Patients with chronic diseases face multiple barriers to adherence with regard to treatment regimens.

1. Time Management: A recent poll on our site identified time management as the #1 barrier to adherence. The CF treatment regimen can take up to five hours a day, and other disease care is similarly time-consuming. Many patients are choosing between doing all their treatments or sleeping, working, going to school…etc.

2. Tracking and Scheduling: Patients often have trouble keeping track of medications and treatments on a daily basis, as well as ensuring there is no gap between refills or loss of functionality of equipment in the long term.

3. Comprehension: Doctors and other medical professionals often have limited time in which to convey treatment information, and patients and caregivers take away a only portion of the instructions or misunderstand them.

4. Lack of Knowledge: Patients are often unaware of all the treatments available to them, and they are often confused about the method of administration of medications and the maintenance of durable medical equipment.

5. Cost of Treatments and Equipment: Patients sometimes lack sufficient finances to cover co-pays for expensive medications, supplements, food and other helpful resources such as exercise equipment or gym memberships.

6. Distance to Appropriate Doctors and Centers: Patients sometimes have to drive 1-3 hours to be treated at a clinic, and they postpone check-ups and admissions due to scheduling or transportation issues.

7. Social Factors: Patients often face awkward or discriminatory social situations with regard to doing treatments in public, the workplace or even with friends. Additionally, CF patients cannot socialize with one another due to the risk of cross-contamination.

8. Mental Health Factors: Stress and depression are more than occasionally cited as reasons patients do not complete their treatments. Depressed or stressed patients may lack motivation or have trouble focusing on the tasks needed to adhere to a complicated and time-consuming treatment regimen.

9. Unsafe Health Facilities: Patients are often hesitant to seek treatment, whether routine or in an acute situation, for fear of acquiring multi-resistant strains of bacteria.

10. Perceived Inefficacy of Treatments: Patients are often misinformed as to when they will see results, or they draw unfounded conclusions regarding positive or negative effects of the medication/treatments. [4]

Tailoring medications for different patients

i. Decreasing the number of daily doses to once or twice a day;

ii. Changing the route of administration, such as using oral medications or transversal patches. and eliminating unnecessary or redundant medications or using combination products when possible.

iii. Decreasing the overall cost of the medication regimen if affordability is a barrier to adherence.[5]

Points to remember when prescribing medicine

i**.** Be warm and caring and respect the patient's concerns, medical treatment goals.

ii. Talk to patients directly about the need for adherence.

iii. Communicate the benefits and risks of treatment in an understandable way that fosters the perception that the patient has made an informed choice about his or her care; and Probe patients about their medicine taking habits and health beliefs.

iv. Obtain agreement from the patient on the specifics of the regimen, including the probe for and help resolve patient concerns up front so they do not become hidden reasons for poor adherence.[5]

Critical information for patients

i. What condition the medicine was prescribed to treat.

ii. What the medicine is, why it is needed and how it works in the body.

iii. Why the medicine was selected

iv. The dosage schedule and related instructions about how to take the medicine (before eating, with food, etc).

v. Whether the medicine will work safely with other medicines being taken (both prescription and nonprescription medicines).

vi. What to do if doses are missed or delayed.

vii. The common adverse effects that may occur and what to do about them.

viii. How to monitor whether the medicine is having its intended effect (are lab tests or blood

work necessary; if so, how often).

ix. Serious adverse effects to look out for and what to do if they occur.

x. What action to take when the prescription is about to run out.[6]

Improving medical adherence

Health care professionals are urged to educate their patients about medicines: why they are taking them, what the medicines look like, what time they should be taken, their potential side effects, what to do if a side effect is experienced, and regular testing that may be required. Patient's medicine uses followed by Figure-2.

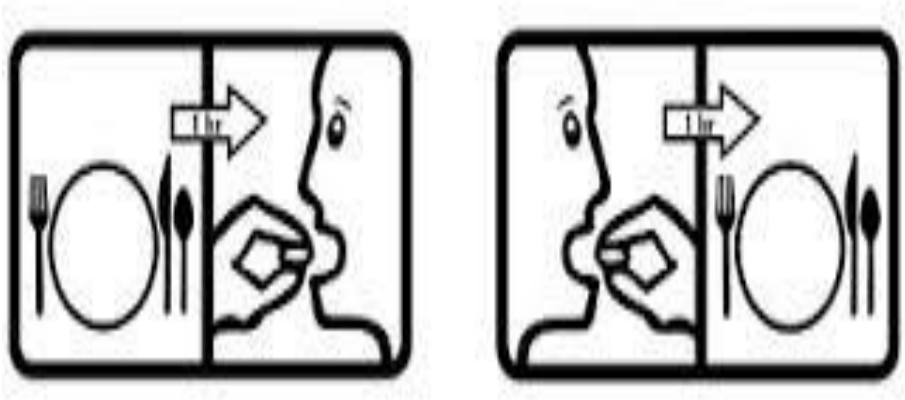

Figure-2: Pictograms help patients to take their medicines as prescribed.

Change in dosing schedule. Taking medicines once or twice daily improves adherence, so whenever possible, such regimens should be established. For ARVs, adherence has increased with the emergence of fixed dosed combination tablets which combine two or three ARVs into one pill, to be taken once or twice daily.[5]

Monitoring adherence with every patient visit to the prescribing health care provider or pharmacist shown in figure-3.

Figure-3: Pill organizers help patients to take their medicines as prescribed.

Providing information verbally and reinforcing these instructions through giving the patient useful written information in language that clearly explains how the patient can manage their medicines. This information may be presented in pictures and should include the exact time medicine should be taken, why and how long to take it and common side-effects.[5]

Improvement of adherence

Adherence can be improved by changing the patient's perception of cost, concerns, and benefits. Cost-related nonadherence (CRN) is a common and critical problem for elderly patients in the outpatient setting who take, on average, four to five medications each week. Recent surveys show that up to 32 percent of MA plan members take less medication than prescribed to lower their costs. But patients who reduce their costs by taking their medications sporadically, splitting pills, or delaying refills do not achieve the full therapeutic benefits of therapy and may be at increased risk of declining health.

There are of course other behavioral factors that also must be addressed. They include the perceived burden of taking medication, concern about side effects, and failure to understand why the medication is needed. All lead to lack of motivation and commitment. Behavioral factors are just as significant as financial costs and also must be addressed.

It is essential that patients fully understand the benefits and be committed to their prescribed therapy. This can be accomplished by using providers able to educate and motivate their patients to comply with their treatment regimen, which means taking full account of a patients' cultural milieu and health care literacy.[7]

Motivational interviewing

The ability of providers to help their patients adhere to their treatment plan can be strengthened through the use of skills related to motivational interviewing. These techniques enhance listening skills and provide tools to help build consensus with the patient regarding treatment plans and medication schedule, ultimately supporting adherence.[7]

Policies that promote adherence

The New England Healthcare Institute (NEHI) and other organizations have cited several opportunities for improving adherence. They include.

I. Health care teams. Although physicians play a key role in improving medication adherence by their patients, the problem is often too complex for the physician alone, necessitating support through the creation of care teams incorporating nurses, care managers, pharmacists and other clinicians either inside or outside the physician's practice. These teams increase the number of touch points for patients, offering repeated checks as they move through the health care system.

II. Patient engagement and education. Counseling by primary care providers and pharmacists to help patients understand their disease and the important role of their medication in improving their condition is critical to motivating patientss.[7,8]

A COMPLETE MEDICAL EVALUATION FOR TB INCLUDES THE FOLLOWING

Medical History

Clinicians should ask about the patient's history of TB exposure, infection, or disease. It is also important to consider demographic factors (e.g., country of origin, age, ethnic or racial group, occupation) that may increase the patient's risk for exposure to TB or to drug-resistant TB. Also, clinicians should determine whether the patient has medical conditions, especially HIV infection, that increases the risk of latent TB infection progressing to TB disease.

Physical Examination

A physical exam can provide valuable information about the patient's overall condition and other factors that may affect how TB is treated, such as HIV infection or other illnesses.

Test for TB Infection

The Mantoux tuberculin skin test (TST) or the TB blood test can be used to test for M. tuberculosis infection. Additional tests are required to confirm TB disease. The Mantoux tuberculin skin test is performed by injecting a small amount of fluid called tuberculin into

the skin in the lower part of the arm. The test is read within 48 to 72 hours by a trained health care worker, who looks for a reaction (induration) on the arm. The TB blood test measures the patient's immune system reaction to M. tuberculosis.

Chest Radiograph

A posterior-anterior chest radiograph is used to detect chest abnormalities. Lesions may appear anywhere in the lungs and may differ in size, shape, density, and cavitations. These abnormalities may suggest TB, but cannot be used to definitively diagnose TB. However, a chest radiograph may be used to rule out the possibility of pulmonary TB in a person who has had a positive reaction to a TST or TB blood test and no symptoms of disease.

Diagnostic Microbiology

The presence of acid-fast-bacilli (AFB) on a sputum smear or other specimen often indicates TB disease. Acid-fast microscopy is easy and quick, but it does not confirm a diagnosis of TB because some acid-fast-bacilli are not M. tuberculosis. Therefore, a culture is done on all initial samples to confirm the diagnosis. (However, a positive culture is not always necessary to begin or continue treatment for TB.) A positive culture for M. tuberculosis confirms the diagnosis of TB disease. Culture examinations should be completed on all specimens, regardless of AFB smear results. Laboratories should report positive results on smears and cultures within 24 hours by telephone or fax to the primary health care provider and to the state or local TB control program, as required by law.

Drug Resistance

For all patients, the initial M. tuberculosis isolate should be tested for drug resistance. It is crucial to identify drug resistance as early as possible to ensure effective treatment. Drug susceptibility patterns should be repeated for patients who do not respond adequately to treatment or who have positive culture results despite 3 months of therapy. Susceptibility results from laboratories should be promptly reported to the primary health care provider and the state or local TB control program.[2,9,10,11]

COMPLETING TREATMENT IS ESSENTIAL

After a few weeks, you won't be contagious, and you may start to feel better. It might be tempting to stop taking your TB drugs. But it is crucial that you finish the full course of therapy and take the medications exactly as prescribed by your doctor. Stopping treatment too

soon or skipping doses can allow the bacteria that are still alive to become resistant to those drugs, leading to TB that is much more dangerous and difficult to treat.

Treating tuberculosis

Treatment for tuberculosis (TB) depends on which type you have, although a long course of antibiotics is most often used. While TB is a serious condition that can be fatal if left untreated, deaths are rare if treatment is completed. For most people, hospital admission during treatment is not necessary.

Pulmonary TB

If you are diagnose with active pulmonary TB (TB that affects your lungs and causes symptoms), you will be referred to a specialist TB treatment team. This is a team of healthcare professionals with experience in treating TB.

Treatment team

Your TB treatment team may include.

I. a respiratory physician – a doctor who specialises in conditions that affect the lungs and breathing
II. an infectious disease specialist
III. a TB nurse
IV. a health visitor – a qualified nurse with extra training who helps families with babies and young children to stay healthy
V. your GP
VI. a paediatrician (if necessary) – a doctor who specialises in conditions that affect children

It is also likely that you will be assigned a key worker. This is usually a nurse, health visitor or social care support worker who will be the point of contact between you and the rest of the team and will help co-ordinate your care.

Antibiotics

Pulmonary TB is treated using a six-month course of a combination of antibiotics. The usual course of treatment is.

I. two antibiotics – isoniazid and rifampicin – every day for six months
II. two additional antibiotics – pyrazinamide and ethambutol – every day for the first two months.

However, you may only need to take these antibiotics three times a week if you need supervision. It may be several weeks or months before you start to feel better. The exact length of time will depend on your overall health and the severity of your TB.

After taking the medicine for two weeks, most people are no longer infectious and feel much better. However, it is important to continue taking your medicine exactly as prescribed and to complete the whole course of antibiotics.

Taking medication for six months is the most effective method of ensuring that the TB bacteria are killed. If you stop taking your antibiotics before you complete the course or if you skip a dose, the TB infection may become resistant to the antibiotics. This is potentially serious, as it can be difficult to treat and will require a longer course of treatment.If treatment is completed correctly, you should not need any further checks by a TB specialist afterwards. However, you may be given advice about spotting signs that the illness has returned, although this is rare.

In rare cases, TB can be fatal even with treatment. Death can occur if the lungs become too damaged to work properly.

Extrapulmonary TB

Extrapulmonary TB (TB that occurs outside the lungs) can be treated using the same combination of antibiotics as those used to treat pulmonary TB. However, you may need to take them for 12 months.

If you have TB that affects your brain, you may also be prescribed a corticosteroid, such as prednisolone, for several weeks to take at the same time as your antibiotics. This will help reduce any swelling in the affected areas. As with pulmonary TB, it is important to take your medicines exactly as prescribed and to finish the course.

Latent TB

Latent TB is where you have been infected with the TB bacteria but do not have any symptoms of active disease. Treatment for latent TB is usually recommended for:

I. people 35 years of age or under
II. people with HIV, regardless of their age
III. healthcare workers, regardless of their age

IV. people with evidence of scarring caused by TB, as shown on a chest X-ray, but who were never treated.

Treatment is not recommended for people who have latent tuberculosis and are over 35 years of age (and do not have HIV and are not healthcare workers). This is because the risk of liver damage increases with age and the risks of treatment outweigh the benefits for some people. Latent TB is also not always treated if it is suspected to be drug resistant. If this is the case, you may be regularly monitored to check the infection does not become active.

In some cases, treatment for latent TB may be recommended for people requiring immunosuppressant medication. This medication suppresses the immune system (the body's natural defense against illness and infection) and can allow latent TB to develop into an active form of the disease. This may include people taking long-term corticosteroids or people receiving chemotherapy.

In these cases, the TB infection should be treated before immunosuppressant medication begins.

Treatment for latent TB involves either taking a combination of rifampicin and isoniazid for three months, or isoniazid on its own for six months.[11]

Side effects of treatment

Rifampicin can reduce the effectiveness of some types of contraception, such as the combined contraceptive pill. Use an alternative method of contraception, such as condoms, while taking rifampicin.

In rare cases, these antibiotics can cause damage to the liver or the eyes, which can be serious. Therefore, your liver function may be tested before you begin treatment. If you are going to be treated with ethambutol, your vision should also be tested at the beginning of the course of treatment.

Contact your TB treatment team immediately if you have any of the following symptoms:

I. feeling sick or being sick
II. yellowing of your skin (jaundice) and darkening of your urine
III. unexplained fever – a temperature of 38ºC (100.4ºF) or above
IV. tingling or numbness in your hands or feet

V. skin rash or itchy skin
VI. changes to your vision, such as blurred vision or colour blindness.

Supervised treatment

Sometimes people find it difficult to take their medication every day. If this affects you, your treatment team can work with you to find a solution. Usually, you will be asked to join a programme of "directly observed therapy".

This can include supervised treatment, which will involve regular contact with your treatment team (daily or three times a week) to support you taking your medication. This can take place in your home, the treatment clinic or somewhere else more convenient.

Antibiotic-resistant tuberculosis (TB)

Like most bacteria, bacteria that cause TB can develop a resistance to antibiotics. This means the medicines can no longer kill the bacteria they are meant to fight.

Tuberculosis (TB) that develops a resistance to one type of antibiotic is not usually a concern because alternative antibiotics are available. In 2011, more than eight out of 100 cases of TB were resistant to at least one type of antibiotic normally used to treat the condition.

However, in a number of cases

I. TB develops a resistance to two antibiotics – this is known as multi-drug resistant tuberculosis (MDR-TB)
II. TB develops a resistance to three or more antibiotics – this is known as extensively drug resistant tuberculosis (XDR-TB)

In 2011, almost two out of every 100 TB cases were resistant to at least two antibiotics.
Both MDR-TB and XDR-TB will usually require treatment for at least 18 months using a combination of different antibiotics. As these conditions are difficult to treat, you may be referred to a specialist TB clinic for treatment and monitoring.

Preventing the spread of infection

If you are diagnosed with pulmonary tuberculosis (TB), which affects the lungs, you will be contagious up to about two to three weeks into your course of treatment.

You will not normally need to be isolated during this time, but it is important to take some basic precautions to stop TB spreading to your family and friends. These precautions are:

I. stay away from work, school or college until your TB treatment team advises you it is safe to return
II. always cover your mouth when coughing, sneezing or laughing
III. carefully dispose of any used tissues in a sealed plastic bag
IV. open windows when possible to ensure a good supply of fresh air
V. do not sleep in the same room as other people because you could cough or sneeze in your sleep without realizing it.

To help people stick with their treatment, a program called directly observed therapy (DOT) is sometimes recommended If you test positive for latent TB infection, your doctor may advise you to take medications to reduce your risk of developing active tuberculosis. The only type of tuberculosis that is contagious is the active variety, when it affects the lungs. So if you can prevent your latent tuberculosis from becoming active, you won't transmit tuberculosis to anyone else.

First-line treatment of TB for drug sensitive TB

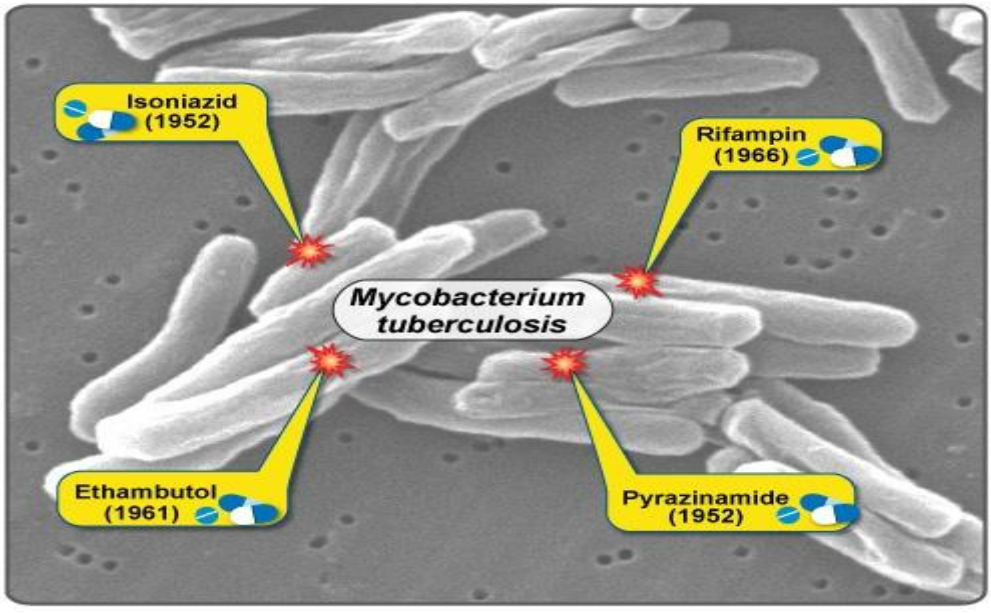

Figure 4: First-line treatment of TB for drug sensitive TB

Tuberculosis, which results from an infection with Mycobacterium tuberculosis, can usually be cured with a combination of first-line drugs taken for several months. Shown here are the four drugs in the standard regimen of first-line drugs (Figure 4).

Multidrug-Resistant TB (MDR-TB)

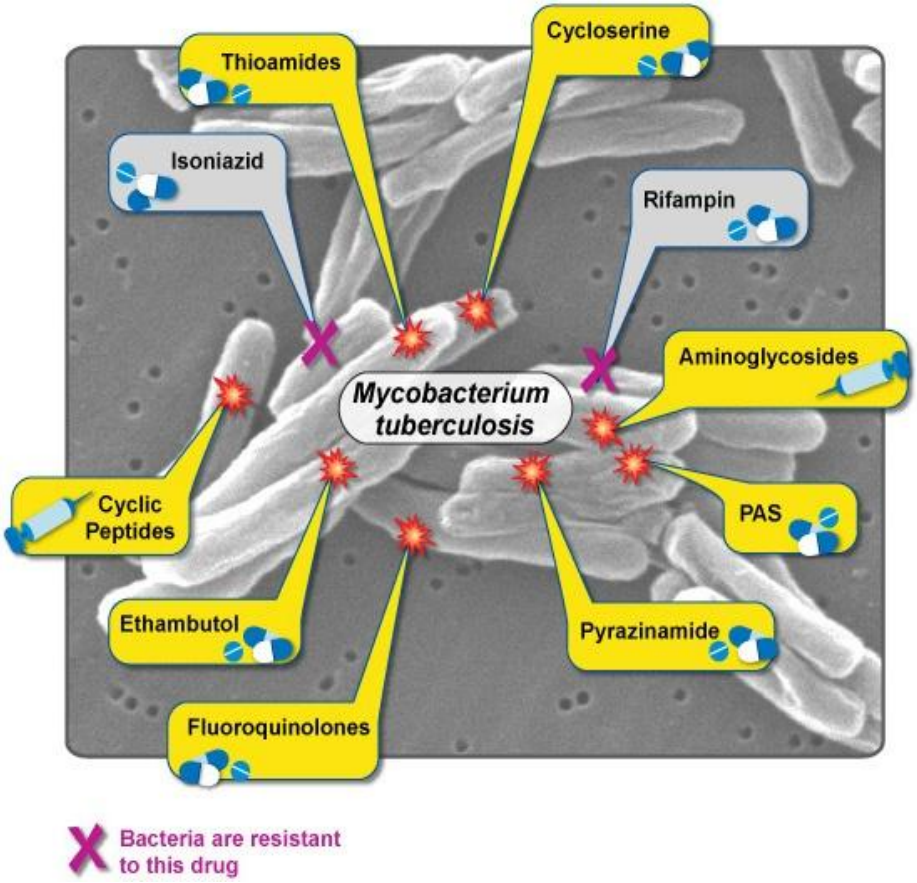

Figure-5: Multidrug-Resistant TB (MDR-TB)

MDR TB occurs when a Mycobacterium tuberculosis strain is resistant to isoniazid and rifampin, two of the most powerful first-line drugs. To cure MDR TB, healthcare providers must turn to a combination of second-line drugs, several of which are shown here. Click here to see how these drugs work. Second-line drugs may have more side effects, the treatment may last much longer, and the cost may be up to 100 times more than first-line therapy. MDR TB strains can also grow resistant to second-line drugs, further complicating treatment (Figure-5).

Extensively drug resistant TB (XDR-TB)

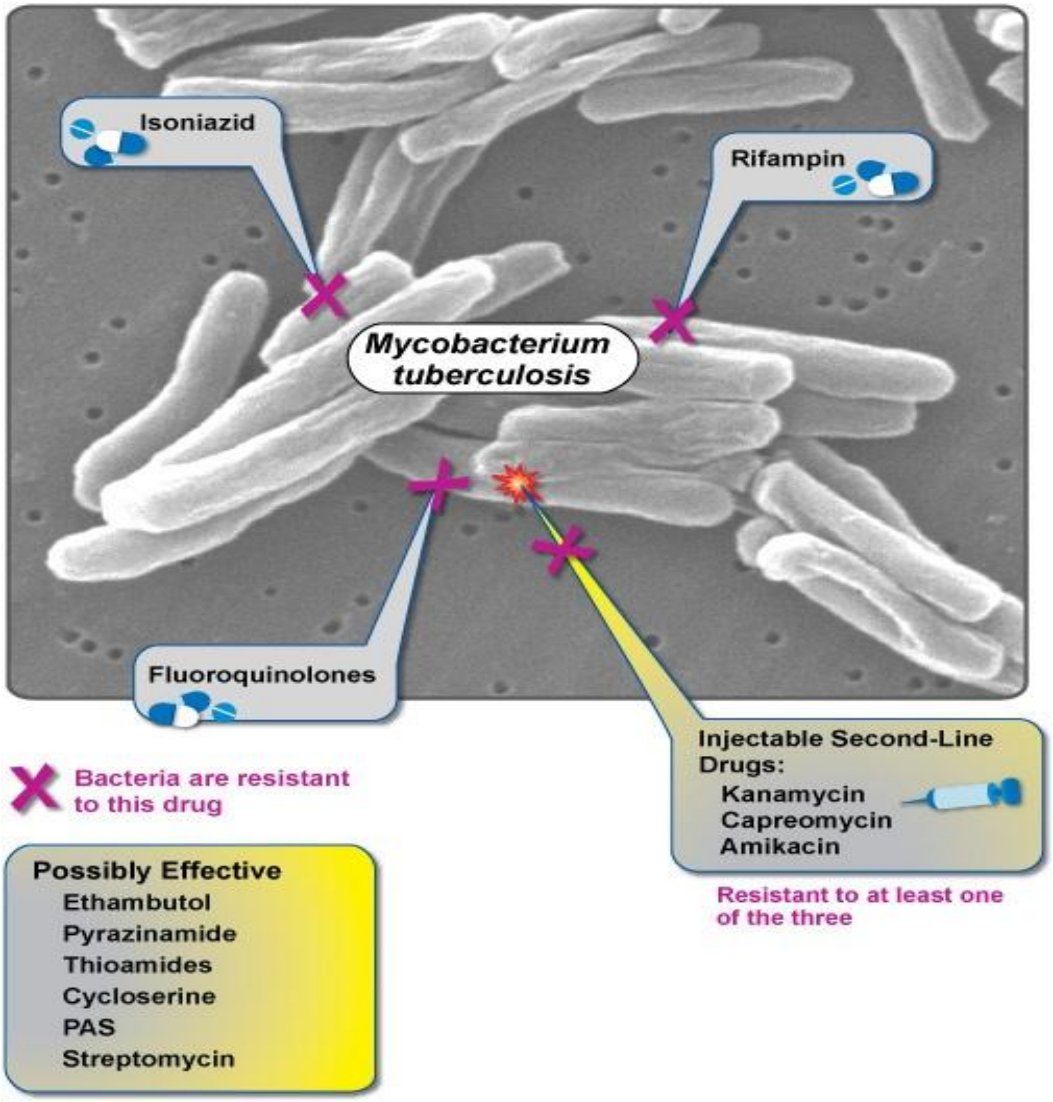

Figure -6: Extensively drug resistant TB (XDR-TB)

XDR TB occurs when a Mycobacterium tuberculosis strain is resistant to isoniazid and rifampin, two of the most powerful first-line drugs, as well as key drugs of the second line regimen—any fluoroquinolone and at least one of the three injectable drugs shown above. XDR TB strains may also be resistant to additional drugs, greatly complicating therapy (Figure 6).

Future TB Drugs Under Development

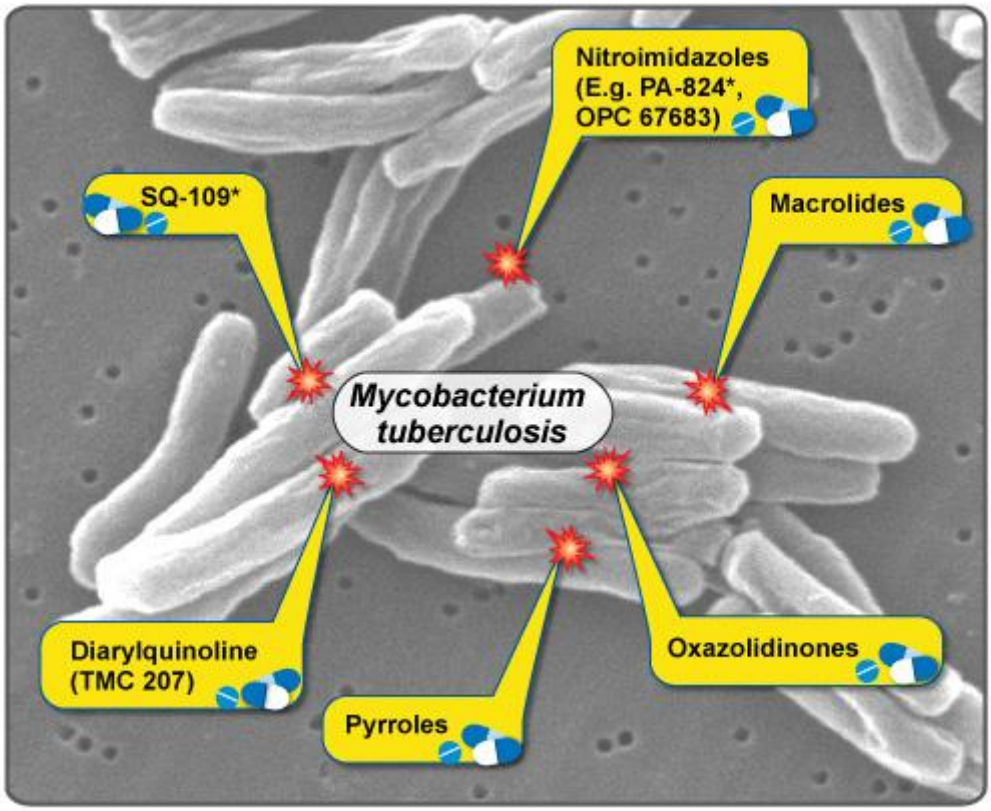

Figure-7: Future TB Drugs Under Development

Several new types of TB drugs currently under development are shown here. NIAID has supported the development of two of these compounds, SQ-109 and PA-824 (Figure-7).[1.12.13]

TUBERCULOSIS IN BANGLADESH

Epidemiology

A national study conducted in 1987 1988 estimated that national adults TB prevalence in Bangladesh was 870 per 100,000 populations. 22 Men were almost twice as likely to have TB as women (prevalence of 1.08% and 0.6% respectively), and TB occurred more frequently in urban areas (1.61%) than rural (0.8%).

By 1997 another community study estimated the prevalence of TB in Bangladesh had dropped to 508 per 100,000 (620,000 cases) and the incidence to 246 per 100,000 (300,000 cases).24 Approximately 68,000 individuals died from TB in Bangladesh in 1997.23 In 2005 the World Health Organization (WHO) estimated that the prevalence had decreased to 406 per 100,000 (576,000) while the incidence remained steady at 227 new cases per 100,000

(340,000 total).iii, 13 Estimated mortality was 47 per 100,000 (75,000 total). In 2004 about 1.8% of new cases (97% of all cases were classified as new) and 14% of previously treated cases were classified as multidrug resistant tuberculosis (MDR TB).

The National TB Program: 1965-1994

The state first initiated TB services in East Pakistan (modern day Bangladesh) in 1965 with 44 TB clinics, 8 hospitals, and 5 TB hospitals providing mainly curative services and anti TB medications at no cost. The World Bank began providing the government consecutive, five year grants for health and population in 1975.26 Of the total USD 600 million awarded by 1998, the government dedicated USD 17.6 million to strengthening and expanding TB and leprosy control services.25 The WHO provided technical and administrative support for the Bank funded programs. By 1991, 124 upazila health complexes were providing TB services.

In 1991 the government began to reorganize its health program and initiated partnerships with NGOs to strengthen TB services. The National Tuberculosis Programmed (NTP) was created within the Directorate Simultaneously, the government hired 10 WHO consultants, eight of whom were Bangladeshi, to help improve TB program operations.25 At the district level the NTP had 40 medical officers, 31 program organizers, and 44 TB consultants, along with almost 300 leprosy and TB control assistants from the upazila level. The WHO provided technical support in procuring microscopes, and the central office consultants procured all drugs to ensure competitive pricing. District level consultants procured and stored drugs from the central office.

Perceiving private services to be of higher quality than government services, many TB patients preferred not to seek treatment at government facilities even when treatment was available at no cost. A estimates of incidence and thus case detection rates are based on the National Prevalence Survey of 1987 1988. Member of the National TB Association (NATAB), a volunteer organization founded in 1948 to promote and mobilize TB awareness and control efforts, explained, “For a long time, there were 44 chest clinics where people could go to get free [TB] medicine. When people went there, they got a few months of medicine, and then the clinic would run out. Many lost confidence in the system.” In most rural areas, pharmacies and traditional healers were the only other options available.

Though no formal evaluation was conducted on the program’s performance, a review for the World Bank in 1990 estimated that case detection in Bangladesh was less than 20% and the

cure rate below 50%. Academic and private facilities were not compelled to report their case detection and cure rates to the NTP.

Implementing the TB Program: 1984-2012

From 1984 to 1989, Ishikawa''s team; primarily Akramul Islam and Dr. Sakhawat Hossain, a pathology professor who was the Secretary General of NATAB; piloted a community based TB program with shebikas in the upazila of Manikgonj. Together they trained 200 shebikas to identify and treat TB. Shebikas learned to conduct house visits and inquire if anyone was experiencing a cough lasting longer than three weeks. If an individual affirmed that condition, the shebika would give him or her two containers for three weeks. If an individual affirmed that condition, the shebika would give him or her two containers for and smearing site, which BRAC would set up in various locations throughout the month. There the BRAC staff would ask the patient to produce an additional sputum sample. These samples were sent to a laboratory for diagnosis based on smear microscopy. During the pilot BRAC relied on the sub district government laboratory facilities, which were equipped with trained technicians and required no additional support from BRAC. However, the laboratories were soon overwhelmed by the influx of sputum smears. When necessary, BRAC sent staff to work on a part time basis to reduce the burden on the government employees. Often, when BRAC approached the local laboratory facilities, the team found that the facility''s staff members were reluctant to collaborate. Once BRAC established a laboratory, the NTP provided training for the staff on how to perform microscopy examinations. This was BRAC''s primary strategy through 1988, when BRAC and the NTP were able to convince the district level governments to actively support the partnership. At that point BRAC began to utilize the government facilities as much as possible but maintained its labs in particularly high burden areas.

After the lab technicians made a primary diagnosis, a physician confirmed the results. The PO relayed the results to the shebika. If the sputum test came back negative but the symptoms persisted, the shebika referred the patient to the upazila health complex or to the district TB clinic. For patients whose results tested positive, the shebika would begin to administer directly observed therapy (DOT). For the first two to three months, the patients would meet her every time they were supposed to take medication, and she would watch them swallow their pills. After that phase of intense treatment, the patients would visit the shebika once a week to pick up their medication and report on symptoms. The POs or shebikas referred

patient's significant side effects or who were not responding to therapy to a BRAC physician for evaluation. If the problem proved too complex, the BRAC physician referred the patient to the upazila health complex or to district TB clinics. During this period, the government provided medication free of charge. At times the government was unable to provide the drugs NATAB or BRAC would buy them. Shebikas received medications on a monthly basis and stored them in their homes. Between 1984 and 1989, 264 patients initiated 12 month DOT treatment; approximately 60% completed treatment, 8% dropped out, and the remainder was lost to follow up (including those who died, moved out of the district, or transferred out).19 The average cost per case was USD 108.

Adjusting and Expanding the Program: 1989-2012

During the pilot, there were several challenges. Patients often ceased treatment once their symptoms decreased. Ishikawa and his team devised a bond system to remedy this issue. Patients would deposit USD 3 and sign a statement before initiating treatment promising to complete treatment or forfeit the bond. Of the USD 3, USD 0.50 went to paying the shebika, and USD 2.50 was returned to the patient when a patient was successfully cured. For a patient to be considered ""cured,"" two conditions had to be met. The patient must have successfully completed the treatment regimen and must have tested smear negative at the completion of treatment. Shebikas were only paid for patients that were successfully cured. In cases where patients were too poor to put down a deposit, BRAC would ask the village to collectively put down a deposit for the patient. When this was not possible, BRAC would waive the deposit (Figure -8).

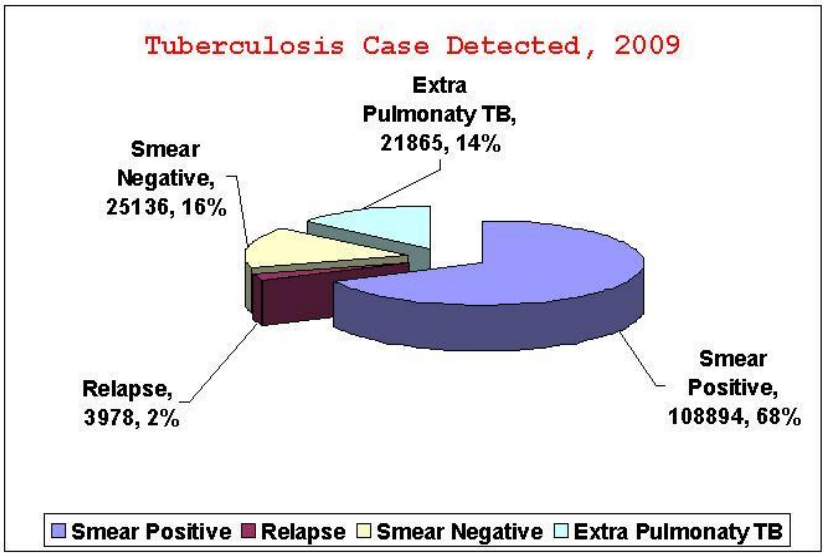

Figure-8: Tuberculosis Treatment Outcome in 2010

National Tuberculosis Control Program, Bangladesh informed that the treatment success was **91%** (cure **90%** and complete **1%**) and unusual outcomes **9%** (died **4%**, failure **1%**, defaulted **2%**, transfer out **2%** and others less than **1%**) among Smear Positive Pulmunary Cases (SS+ve) of cohort 2009.[14]

Incidence of tuberculosis (per 100,000 people) in Bangladesh

Incidence of tuberculosis (per 100;000 people) in Bangladesh was last measured at 225 in 2012, according to the World Bank. Incidence of tuberculosis is the estimated number of new pulmonary, smear positive, and extra-pulmonary tuberculosis cases. This page has the latest values, historical data, forecasts, charts, statistics, an economic calendar and news for Incidence of tuberculosis (per 100;000 people) in Bangladesh (Figure-9).

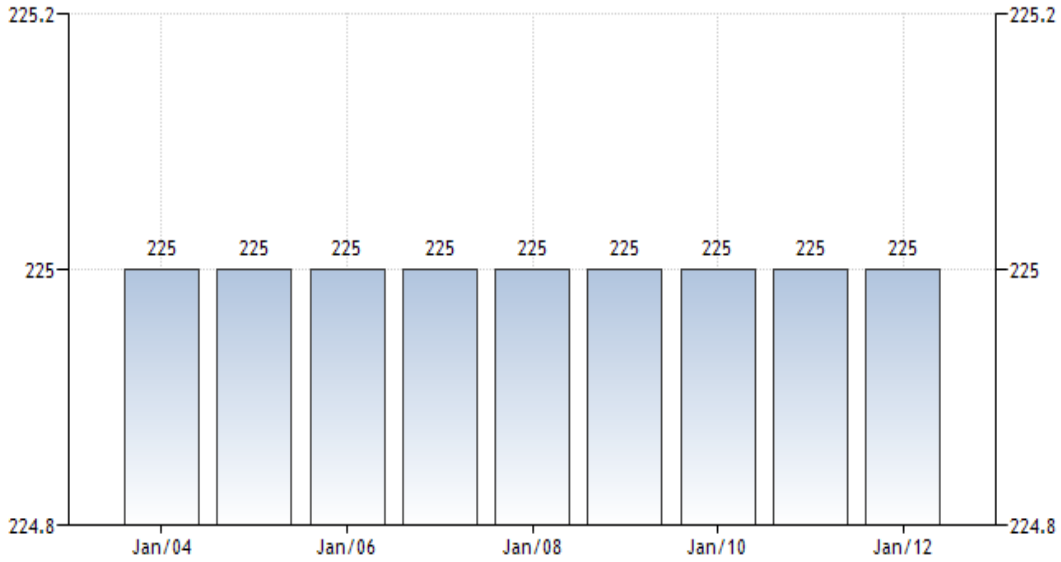

Figure-9: Schematic graph on TB incidence

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.

Age

Between 1993 and 2011, TB case rates have decreasedamong all age groups with declines of 40 to 65%. TB case rates generally increased as age increases; the 0-14 age group had the lowest case rate at 0.9 per 100,000 in 2011 while those over the ageof 65 had the highest at 5.4 per 100,000.

Sex

Males were 62% more likely than females to have TB (4.2 vs. 2.6 per 100,000). Between 1993 and 2011, TB incidence decreased by more than 50% in both men and women; however, the decrease was greater among males than females.TB case rates by sex from 1982 through 2010.[14]

ADHERENCE OF TB MEDICINE IN BANGLADESHI PATIENT

Tuberculosis is the second most common cause of death from infectious disease (after those due to HIV/AIDS). The absolute number of tuberculosis cases ("prevalence") has been decreasing since 2005, while new cases ("incidence") have decreased since 2002. Bangladesh has achieved particularly dramatic progress, with an approximate 60% reduction in its TB mortality rate between 1990 and 2010. Tuberculosis is more common in developing countries; about 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5–10% of the US population test positive. Hopes of totally controlling the disease have been dramatically dampened because of a number of factors, including the difficulty of developing an effective vaccine, the expensive and time-

consuming diagnostic process, the necessity of many months of treatment, the increase in HIV-associated tuberculosis, and the emergence of drug-resistant cases in the 1980s.

In 2005, the country with the highest estimated incidence rate of TB was Bangladesh, with 1,200 cases per 100,000 people. India had the largest total incidence, with an estimated 2.0 million new cases. In developed countries, tuberculosis is less common and is found mainly in urban areas. Rates per 100,000 people in different areas of the world where: globally 178, Africa 332, the Americas 36, Eastern Mediterranean 173, Europe 63, Southeast Asia 278, and Western Pacific 139 in 2010. In Canada and Australia, tuberculosis is many times more common among the aboriginal peoples, especially in remote areas. In the United States the Aborigines have a fivefold greater mortality from TB, and racial and ethnic minorities accounted for 84% of all reported TB cases.[3,14]

NATIONAL TB CONTROL PROGRAM (NTP)

The overall goal of the NTP is to reduce morbidity, mortality and transmission of TB until the disease is no longer a public health problem.

The objectives are to detect 70% of new smear-positive pulmonary TB cases and cure at least 85 % of them by the year 2005 and be maintained thereafter to reach the MDG by 2015.

DOTS strategy

The NTP adopted the WHO recommended strategy of Directly Observed Treatment Short-course (DOTS) in 1993.The DOTS strategy consists of five components:

- Political commitment
- Diagnosis by direct microscopy
- Directly Observed Treatment (DOT)
- Uninterrupted supply of drugs
- Standard recording and monitoring of detection and treatment results (Figure -10).

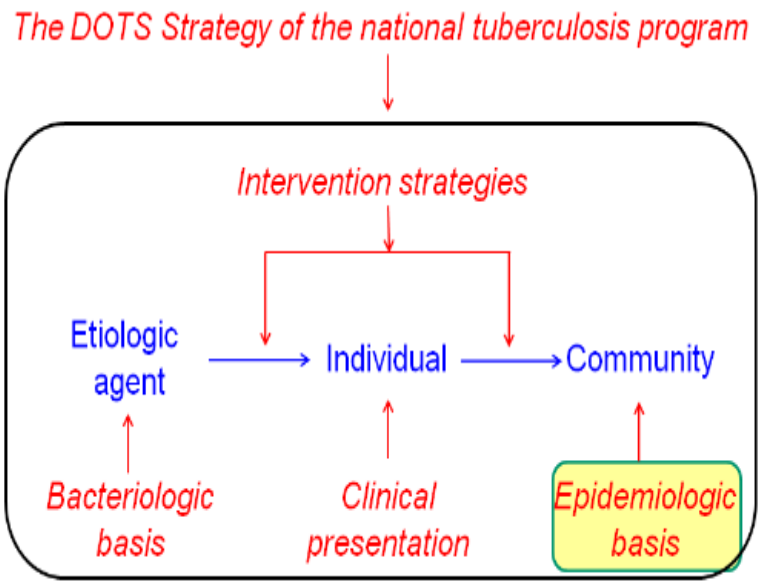

Figure -10: The DOTS strategy of national TB program.

Achievements

Since the introduction of DOTS the NTP and its partners have achieved satisfactory treatment results in new smear-positive patients, 84% treatment success among the patients detected during 2001. However, case detection has remained under 35%. During 2004 the detection rate of new smear-positive patients was 46%.During 2005 the detection rate of new smear-positive patients was 61% and treatment success rate 89%.

RECENT DEVELOPMENTS

Treatment

I. Change in regimen for new smear-positive and for smear-negative and extra-pulmonary patients, as follows:
II. Regimen for new smear-positive patients and other severely ill patients: 2HRZE/4H3R3
III. Regimen for relapses and failures : 2SHRZE/1REHZ/5R3E3H3
IV. Regimen for smear-negative and extra-pulmonary patients: 2HRZ/4H3R3
V. Change in formula of the drugs, from loose drugs to fixed dose combinations (FDC's) of 4 drugs (smear-positive patients), 3 drugs (smear-negative and extra-pulmonary patients) and 2FD's (all patients during the continuation phase of the treatment).
VI. Provision of FDC's in blister packs. After diagnosis the full treatment of the patient will be set aside.

VII. Continuation of a pilot project on public-private partnership, involving 63 chest physicians and general practitioners in Dhaka City.

VIII. Public Private Partnership Project, an operational research project collaborated between NTP and Nuffield Institute for Health, University of LEEDS, UK started its activities in March, 2004. This project is aimed to develop an innovative partnership model for effective involvement of private practitioners in service delivery of the TB control activities in Bangladesh.

IX. DOTS expansion in Dhaka and other metropolitan cities. After detailed preparation and training of staff, the number of diagnostic and treatment facilities in Dhaka and other city corporations has been increased.

X. Opening of new DOTS corners in medical colleges

XI. Opening DOTS Centers at work places.

XII. Expansion of DOTS in prisons.[[15,16]]

PROJECTS CONDUCTED ON TB IN BANGLADESH

USAID TB CARE II program

The TB CARE II Bangladesh project is a field support activity funded through the USAID TB CARE II Project, which is a five year cooperative agreement awarded to the URC led consortium in September, 2010. The project, drawing on the Global Fund and the Government of Bangladesh expert resources, facilitates implementation of strategies to strengthen and expand TB DOTS, Programmatic Management of Drug Resistant TB (PMDT) programs, and health systems.

Aligned with National TB Control Programme strategic objectives and USAID/Dhaka strategic framework, the TB CARE II partnership's activities complement the Global Fund and Government of Bangladesh efforts to strengthen all the components of Stop TB Strategy with a major emphasis on universal and early access to TB services, Programmatic Management of Drug Resistant TB (PMDT), and health systems strengthening. In the past 2 years the TB CARE II Project made significant achievements in fighting against TB in Bangladesh. Key achievements include: improved access to quality TB and MDR-TB Services, Laboratory Quality Assurance, Development of cPMDT Standard Operating Procedures, strengthening of social support services for MDR TB patients and strengthened support systems for the effective delivery of TB services at all levels.

TB CARE II, through lead implementer URC, will work closely with the Government of Bangladesh and the NTP to strengthen the country's comprehensive response to the disease and build local capacities to.

- Improve universal access to TB diagnosis and treatment as a critical means of reducing TB-related morbidity and mortality;
- Work with GOB to reach and sustain the global targets of > 70% case detection and > 85% cure rates under DOTS;
- Provide high quality DOTS through all levels including PPM;
- Increase access to MDR TB prevention and treatment through community-based approaches; and
- Strengthen diagnostic capacity for drug susceptible and drug resistant TB.

TB CARE II mHealth

With the support of the USAID TB CARE II project, the National Tuberculosis Control Program (NTP) in Bangladesh initiated a Community-based Programmatic Management of Drug Resistance Tuberculosis (cPMDT) program to treat DR TB in 2011. The cPMDT program requires an initial 1-2 months of hospitalization for DR TB patients who are then transitioned to community based care, allowing patients to receive DR TB treatment in their own community. After introduction of cPMDT, a large number of DR TB patients are now being discharged after a short stay in hospital. At the community level, these patients continue their treatment under the supervision of specially trained DR TB DOT (directly observed treatment) providers. Treatment for DR TB requires a complex drug regimen which needs to be maintained over years. The TB CARE II project has developed and introduced a TB mHealth application which is designed to support the DOT providers to ensure quality DOT, assist to quickly identify drug related side effects and link patients to treatment, and above all assist in patient management by facilitating documentation of the management procedures. The mHealth application is a web based monitoring tool which allows DOT providers and managers to keep track of services delivered and organize an electronic record of treatment history of the DR TB patients. This system is designed to get input from mobile devices used by the DOT providers (Smart phone) through a GPS enabled mobile application. There is several NGO's working on Tuberculosis, and they have many programs.[2,15,16]

CONCLUSION

Adherence to the long course of TB treatment is a complex, dynamic phenomenon with a wide range of factors impacting on treatment-taking behavior. Patients' adherence to their medication regimens was influenced by the interaction of a number of these factors. The findings of my review could help inform the development of patient-centered interventions and of interventions to address structural barriers to treatment adherence.

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