ANALYZING THE BENEFIT-COST RATIO OF INTERVENTIONS TO IMPROVE THE OUTCOMES FOR THOSE WITH DRUG-SUSCEPTIBLE AND MULTI-DRUG RESISTANT TUBERCULOSIS

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Benefits and Costs of Controlling the Spread of Drug-Resistant Tuberculosis in Bangladesh

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Analyzing the benefit-cost ratio of interventions to improve the outcomes for those with drug-susceptible and multi-drug resistant Tuberculosis (MDR-TB)

Bangladesh Priorities

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Background

Tuberculosis (TB) is a serious public health problem in Bangladesh. Bangladesh ranks 6th globally in terms of the burden of TB on the population. According to the World Health Organisation, around 350,000 Bangladeshi's developed TB in 2013 and around 80,000 die from TB every year. Tuberculosis therefore accounts for just under 9% of the deaths in Bangladesh every year. Hence, every hour, nine people die of TB in Bangladesh, despite an effective treatment being available.

The economic case for sustained investment in tuberculosis (TB) control in Bangladesh is compelling. Put simply, TB treatment is low cost and effective, and this combination results in substantial economic return. Moreover, the delivery of high quality TB services can also prevent the spread of the disease to others and slow the emergence of multidrug- resistant TB (MDR-TB), a dangerous and costly form of TB. Investment in TB is also important from a poverty reduction perspective, where loss of earnings may force those with TB further into poverty in Bangladesh.

This paper presents the economic case for substantially increasing investment in TB control in Bangladesh. It focuses on two interventions. The first intervention is to expand and scale-up the diagnosis and treatment of drug susceptible TB: the most common form of TB, and one which is responsive to a low cost standard treatment regimen. The second intervention focuses on the treatment of MDR-TB. As the treatment of MDR-TB can be costly, the analysis examines three options: treatment according to current guidelines, treatment should a shortened MDR-TB drug regimen be approved, and community based treatment of MDR-TB. In summary, this paper outlines the costs and benefits of investment of these different TB control interventions in Bangladesh, exploring whether TB control should be a priority investment in the country.

An introduction to TB and TB control in Bangladesh

In simple terms the disease of TB has two stages. The first is *latent TB* infection, when a person first becomes infected with TB. Of those infected, approximately 5% develop *active TB* disease (become TB cases) within 18 months, followed by a further 5% risk of developing active TB disease over a lifetime [1]. The risk of developing active TB (hereafter referred to as TB) increases substantially following HIV infection [2]. Active TB can be broadly divided into two types: TB which is drug- sensitive – responding well to a standard combination first line treatment; and, multi-drug resistant TB (MDR-TB) which is resistant to two or more drugs in the first line standard TB regimen.

Identifying those with active TB is complex. The symptoms of (active) pulmonary TB include cough, fever, night sweats and weight loss, many of which are similar to symptoms of other common diseases. Currently, almost half of all cases of TB go unrecognised in Bangladesh. This case detection rate in Bangladesh remains higher than the global average [3], but still is long way off the global targets agreed by the World Health Assembly. As with most TB programmes, Bangladesh relies primarily on 'passive case finding' to identify most cases of TB. This strategy is based on the expectation that those with TB symptoms will present at health services for their symptoms, and that health professionals are sufficiently skilled to recognise and act on them.

However passive case detection is not the only case detection approach in Bangladesh. In some areas community health workers (CHWs) are also trained to identify those at risk of TB [4]. For example the Bangladeshi Rural Advancement Committees (BRAC's) approach for TB diagnosis and treatment includes community level education and engagement. The programme works with different stakeholders of the community to engage them in efforts to identify patients, ensure treatment adherence, and reduce stigma. Stakeholders can include cured TB patients, local opinion and religious leaders, girls' guides and scouts, other NGO workers, village doctors, pharmacists and private practitioners.

Bangladesh also faces an additional challenge due to the unequal access of the poor to TB services. Despite the economic progress that Bangladesh has made in recent years, it still remains a very poor country, with some 20 per cent of people in Bangladesh living in extreme poverty. In general the use of health services in Bangladesh is far greater for higher income groups compared to low income groups. This is in contrast to the fact that the prevalence of TB is substantially higher in the poorer compared to higher income groups in Bangladesh. The prevalence of TB is estimated to be 5 times higher in the poorest quarter of population compared to the richest quarter [5]. Yet despite this, among TB cases detected in Bangladesh, more than half of them are from richest half of the population with only 2% the found in the poorest quarter [6].

Once a person has been identified by health services as possibly having TB there are a number of different methods available to diagnose active TB. Smear microscopy is recommended by the WHO and is widely used In Bangladesh, often as a 'point of care', low cost, method of TB diagnosis. Those who have positive smear test, are described as having 'smear positive' TB. However, microscopy is far from a perfect test, and may miss substantial numbers of those with active TB [7, 8]. Since 2011, the WHO therefore recommends the Xpert MTB/RIF assay for widespread use in the diagnosis of TB. Xpert MTB/RIF increases chances that a case of TB can be diagnosed [9], and can identify potential cases of

MDR-TB, however the cost per test is considerably higher than that of smear microscopy [10]. In neighbouring countries, such as India, Xpert MTB/RIF is not used on all patients, and is primarily used for those patients who have failed their first course of treatment, and need to be re-treated.

The diagnosis of MDR-TB provides additional challenges. Xpert MTB/RIF can identify cases of rifampcin-resistant TB, a strong indication that a patient has MDR-TB. However, to confirm MDR-TB, culture based tests also are also required, including tests to identify which drugs remain effective (drug susceptibility testing (DST)). However, cultures and DST require substantial laboratory infrastructure, and even very short gaps in between the patient going to be tested for TB and receiving the test result can lead to high levels of default during the MDR-TB diagnostic process [11].

The treatment of drug susceptible TB involves delivering a standard regimen of TB treatment usually for six months, divided into two phases, and intensive phase for two months and a four month continuation phase. During both phases treatment must be adhered to maximise treatment success and prevent drug resistance developing. In the last twenty years the WHO has recommended the Directly Observed Treatment Strategy (DOTS). Twenty years ago, most countries, including Bangladesh hospitalised TB patients to ensure treatment adherence, but this was expensive and did not result in high treatment success rates [12, 13]. Today TB treatment is delivered through a wide range of different ambulatory approaches, with high levels treatment monitoring by health workers. DOT delivery at BRAC clinics is almost exclusively community based, with treatment delivered by community based female volunteers known as shasthya shebikas (SS).

There are 86,000 of these volunteers in Bangladesh, with each one covering 250-300 households. Along with other responsibilities in maternal and child health the SS make daily visits to 10-20 households and when a patient is diagnosed with TB, the SS becomes responsible for DOT delivery for that patient. In government run clinics and some BRAC sites DOT may be facility based, where the patient must return to the health facility on a daily basis to receive DOT. Finally, BRAC and the government work together so that TB diagnosis and treatment initiation occurs at the government run site and patients are subsequently referred to BRAC sites for community based DOT.

With this good treatment monitoring, and high adherence, TB treatment is very successful, with over a 92% cure rate in Bangladesh. Unfortunately, the treatment of MDR-TB is far more complex than first-line treatment and still requires some hospitalisation. It can take 24 months or longer. It is also much less effective than first line treatment and the success rate of MDR-TB treatment in Bangladesh is around 68% [14, 15].

Finally, despite the high success rate of first line treatment, TB treatment can still cause poor households substantial economic loss. Officially TB treatment is provided for free, but studies in Bangladesh consistently show that having TB can be catastrophic to poor households. The costs of TB have been estimated at being somewhere between 11,700 and 19,500 taka a household. Although in some settings direct travel costs are kept low by community treatment observation, lost earning and costs for nutritional support can be significant. Therefore the provision of social protection and cash transfers to TB patients in Bangladesh, may enhance the adherence to treatment, and help mitigate the impact having TB has for those who are already extremely poor [16] [17].

Intervention 1:
Expanding the diagnosis and treatment of drug susceptible TB

Defining the intervention

The key to expanding TB control in Bangladesh is to identify more persons who need testing for TB and link them to effective TB treatment services. However, this is no easy task, given the reach of the 'public' system in Bangladesh is limited. Investment is therefore required to expand access to TB services by linking with private and informal providers to identify and treat (or refer for TB treatment) effectively [18, 19]. In addition strengthening community services and outreach is likely expand and enhance TB case finding. This expansion needs to be supported by strengthening diagnostic capability (which requires substantial support to laboratories and all the systems that support them, including systems to transport samples and quality control services). For treatment, ensuring that treatment success can be maintained as the services are expanded will remain a challenge. Adherence support remains essential. Programmatic, management and information support to all these services needs to have the capacity to enable and support these investments and ensure that funding is spent in an efficient manner [18, 19].

In detail, first focusing on expanding TB case detection through the private sector, a national survey examining care seeking trajectories of those with TB found that 44% of those with TB first sought care from an informal provider, with many not accessing the publically provided free treatment thereafter. Furthermore, a study by Rifat and colleagues [20] examined the role of informal providers in delaying access to TB services. The authors found that, where those persons with TB had first visited informal providers, the care seeking delay was shorter than for those persons who first accessed formal providers. However, thereafter there was substantial delay in linking to free and effective TB treatment. As this study only examined those who eventually accessed care, it is plausible that care

seeking delay is higher amongst all TB cases. Bangladesh may learn from other South Asian countries where links to the informal and private providers has proved pivotal in addressing low TB case detection [21]. In particular, there a number of public-private mix models in India, that provide the basis for identifying both the best model and costs of expanding access to high quality TB treatment through private sector engagement[22].

The other intervention option for expanding access is the extension of community programmes. A recent study of the TB knowledge of key community members found that, while awareness of TB was high, and levels of knowledge that it was curable and infectious were also high, there were gaps in knowledge about how TB was transmitted and considerable stigma around TB [23]. The national TB prevalence survey in 2012 also found similar gaps in knowledge [24], with a lack of knowledge around transmission, symptoms other than cough and the availability of free treatment. Previous economic work from Bangladesh, highlighted the high cost-effectiveness of using community health workers to improve knowledge around TB, identify cases and supervise treatment as an approach to improving TB case detection [4]; indicating that expanding a community based approach may be a promising way forward. In addition, a recent study also emphasised the importance of ensuring that community workers link to the right TB treatment provider [25]. This study emphasised that while a great number of those are referred for treatment, many do not report to the referral treatment centre. This study highlights the need to ensure that case detection, diagnosis and treatment are located in a way that address barriers to access and support, particularly for poor TB patients along the detection, diagnosis and TB treatment cascade.

Estimating costs and benefits of the intervention

The costs of expanding case detection (and the follow-on diagnosis and treatment) were estimated by referring to several published and unpublished costing efforts. For the costs of community case finding we refer to a currently submitted study by Zwerling et al, which was conducted in 2014 examining community based case finding and treatment. For the costs of the public private mix we use an older study conducted in India [22]. This study found that that the costs of the public private co-operation were low, and in effect a transfer payment (not a cost) between the public to private sector that enabled an improvement in treatment quality. The cost of administering the system was therefore included, but not the price of the transfer payment.

The population in need was estimated based on the WHO report 2015 and treating 90% of all TB cases. In total, the analysis here is based on reaching a target of treating just over 120,000 cases of TB over and above the currently treatment of around 190,000 cases.

To estimate the numbers needing to be screened per TB case found we referred to Zwerling et al. that estimate the numbers of those screened to the proportion of those tested and then moving on to treatment. In summary, it was estimated that the prevalence of TB in those screened was currently around 5% (ie. 20 people need to be screened to identify one case of TB). We doubled this, assuming that it would be more difficult to identify the population that needed to be screened to detect TB cases currently undetected. Of those screened, we assumed based on current testing data that one in 10 would be sufficiently symptomatic to require a TB diagnostic test.

We estimate DALYS averted using: a mean age of onset of disease of 45; standard age specific life expectancies; a mix of smear positive and smear negative TB as reported in the WHO global TB report 2015; no age weighting, 2013 Global Burden of Disease (GBD) disease weights. Importantly, to calibrate to the WHO estimates of TB mortality in Bangladesh we had to assume that those who are currently not identified and reported as TB cases have a 50% cure rate. The 50% was arrived at, on the basis of that 25% naturally self-cure, whilst 25% access some poor quality treatment in the informal sector that goes unreported. We identified no transmission model calibrated to Bangladesh so we made a simple assumption (based on expert opinion) that for every one case of TB averted, the most conservative approach would be to assume we prevent one additional case. In line with the Copenhagen Consensus recommendations we value a DALY averted at US$1235 or one gross domestic product (GDP) per capita.

Estimates were validated against previous studies. There have been two studies conducted examining the costs and health returns in Bangladesh. These studies have shown that it currently costs somewhere around US$100 to diagnose and treat a patient with standard drugs in Bangladesh, depending on the mode of treatment delivery. Ten years ago the cost per patient cured was US$ 64 in the BRAC area and US$ 96 in government facilities.

Intervention 2:
Improving outcomes for those with MDR-TB

Defining the intervention

The treatment of MDR-TB has poor outcomes, is complex and can be costly [14, 15, 26]. While MDR-TB can be spread and circulated among populations, its origins lie in the misuse, poor delivery and adherence of TB treatment [27]. Bangladesh is classified by the World Health Organisation (WHO) as having a high MDR-TB burden, with around 4700 cases notified every year. Although the transmission of MDR-TB may be low in Bangladesh, it may be increasing, highlighting the importance of integrating and working with the private and informal providers to ensure that TB cases who fail first line treatment are treated appropriately [28]. A recent study found that almost 17% of case who were referred to MDR-TB diagnosis did not get diagnosed and a further 21% did not start treatment. This was particularly the case for those on low incomes and daily wage labourers. Therefore, as with first line treatment, improving MDR-TB outcomes will rely on systems strengthening to improve sputum transport and the ability of health workers to initiate MDR-TB diagnosis and engagement with the private sector. However, even with these actions the diagnosis and treatment of MDR-TB remains expensive and lengthy. Expanding MDR-TB treatment to the population in need may therefore be considered unaffordable by some. This assessment paper therefore also examines to options in addition to standard MDR-TB treatment: a) implementing shortened MDR-TB regimens and b) decentralising MDR-TB care to the community.

New shortened TB regimens

New shortened MDR-TB regimens hold promise for reducing both costs and improving impact; and thus may make MDR-TB treatment both a more affordable and cost-effective intervention. However currently the WHO position is that the evidence base is insufficient to support widespread global adoption of these regimens – and therefore at this point in time these regimens are only recommended within the context of research and under close monitoring. This recommendation has been carefully considered, and is based on the fact that there currently is no high quality evidence that shortened MDR-TB regimens are effective. There are a number of weak quality studies that have taken place, but none of these have the design sufficient to convince global experts that widespread use is desirable. A particular concern is that those patients who do well initially may later acquire resistance. In the particular case of Bedaqualine based shortened regiments, the first clinical trials had high death rates, which could not be established to be coincidental, so further carefully monitored trials are required before it will be recommended for widespread use in the treatment of MDR-TB.

Having said this, early studies on shortened MDR-TB regimens have demonstrated sufficient promise that there has been substantial recent investment in large multi-country clinical trials. These are expected to report results in the near future. In particular, Bangladesh was a forerunner in one of the earliest cohort studies that suggested that these shortened regimens may be effective [29]. In particular, a Gatifloxicin based regimen showed some promise (now known as the 'Bangladesh regimen'). While the study design was not considered sufficient to justify widespread recommendation for adopting this regimen, the cohort receiving this regimen has reported short term and long term outcomes. This regimen is a 9-month regimen using gatifloxicin, clofazimine, ethambutol and pyramizide, supplemented by prothionamide, kanamycin and high dose isoniazid during an initial 'intensive' phase of a minimum of 4 months. Under study conditions this results in a treatment success of around 88%. A later follow-up study found that this success was largely maintained two years following treatment completion [30]

Due to these promising nature of the results , a clinical trial, the STREAM trial is now underway [31]. The aims of the STREAM trial are to evaluate the efficacy and safety of the 'Bangladesh regimen' compared to the current WHO-recommended standard of care. In addition, a new bedaquiline-containing regimen is also being examined. The first stage of this trial is due to report in 2017, and will have a full economic evaluation as part of its reporting.

Community based MDR-TB treatment

Given the current expense of MDR-TB treatment, several countries are now decentralising MDR-TB treatment [32]. This has shown to reduce costs, although evidence on whether this is approach is effective is still emerging. As with shortened regimens, this is an approach that needs to be carefully supported, monitoring and evaluated before widespread adoption. In particular in Bangladesh there are pilots examining the use of community care for the later treatment stages of MDR-TB, but with strengthen supervision and medical monitoring.

Estimating the costs and benefits of the intervention

There are however no studies examining the costs of MDR-TB treatment in Bangladesh, but there have been studies recently conducted in Nepal that estimate that the treatment of those with MDR-TB can cost around US$4000 per person. For this paper costs were estimated using a mix of sources. WHO CHOICE costs were used to estimate the cost of an inpatient bed-day. Costs of diagnostics, outpatient and community support were taken from the first line treatment cost studies above. The costs of different drugs regimens were calculated using the WHO planning and budgeting tool. As with drug-susceptible TB the population in need of MDR-TB treatment is based on the WHO 2015 report, and a

target of treating 90% of all MDR-TB cases. This means that our estimates are based on treating just of 4,700 cases of MDR-TB, around 4,000 more than are currently being treated.

The same methods as described above were used to estimate DALYS averted, adjusted for different cure rates and duration of disease. Importantly, based on the STREAM trial design (non-inferiority) we assumed that standard care, shortened treatment and community based treatment have equivalent outcomes.

Results

The table below shows the total costs and total benefits for one year across the population of Bangladesh of each intervention. These costs and benefits are incremental to current TB programme costs. Investment in intervention 1, including standard treatment for MDR-TB cases results in a BCR of between 12.91 and 20.60. If one examines a scenario where MDR-TB cases are treated using a shortened regimen (intervention 2A) then the BCR increases to 13.44 to 21.45. This further increases if using a community based regimen for MDR-TB to 14.03 to 22.39.

We also show below the BCR separated for different patient groups. If we are just examining the increased detection, diagnosis and treatment of drug susceptible TB patients the BCR (intervention 1 for DS-TB only) we find the BCR increases to 15.30 to 24.40. If looking at MDR-TB cases only it falls, and ranges between 1.81 and 5.34 depending on the discount rate and treatment intervention option.

	3% Discount Rate			5% Discount Rate			10% Discount Rate		
Intervention	**Benefit**	**Cost**	**BCR**	**Benefit**	**Cost**	**BCR**	**Benefit**	**Cost**	**BCR**
All TB									
Intervention 1	$2,211,310,833	$107,319,837	20.60	$1,916,463,109	$107,319,837	17.86	$1,385,604,116	$107,319,837	12.91
Intervention 2a	$2,211,310,833	$103,067,746	21.45	$1,916,463,109	$103,067,746	18.59	$1,385,604,116	$103,067,746	13.44
Intervention 2b	$2,211,310,833	$98,748,771	22.39	$1,916,463,109	$98,748,771	19.41	$1,385,604,116	$98,748,771	14.03
DS-TB only									
Intervention 1	$2,155,623,211	$88,327,633	24.40	$1,868,470,394	$88,327,633	21.15	$1,351,279,142	$88,327,633	15.30
MDR-TB only									
Intervention 1	$55,687,622	$18,992,204	2.93	$47,992,715	$18,992,204	2.53	$34,324,974	$18,992,204	1.81
Intervention 2a	$55,687,622	$14,740,113	3.78	$47,992,715	$14,740,113	3.26	$34,324,974	$14,740,113	2.33
Intervention 2b	$55,687,622	$10,421,138	5.34	$47,992,715	$10,421,138	4.61	$34,324,974	$10,421,138	3.29

We conclude that the economic case for improved and expanded TB control is strong, even excluding the substantial long term benefits of reduced anti-microbial drug resistance). Not only is TB control a sound investment, its benefits will primarily accrue to the very poorest. TB control continues to be chronically under-funded in Bangladesh, yet the costs of addressing TB are not substantial compared to other development and health investments. The economic case for strengthening the health systems and services to support TB control presented here is therefore one of the most convincing in the area of public health today – and TB control should be a core part of future development effort in Bangladesh.

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