

# Research Priorities for TB Control in the South-East Asia Region

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## 1. INTRODUCTION

While significant progress has been made through the application of the DOTS strategy in the eleven countries of the WHO South-East Asia Region<sup>1</sup>, national TB control programmes continue to face a number of challenges. These challenges relate to health systems constraints, chiefly, insufficient numbers of skilled staff at the various levels of national health systems, weak laboratory networks and surveillance mechanisms, and inadequate infrastructure and logistics support. At the same time, low community awareness<sup>2</sup>, poor health seeking behavior<sup>3</sup> and widespread utilization of private sector services that are not linked to the national programmes are recognized as major impediments to improving case detection and treatment success. Establishing and then sustaining interventions for the more complex forms interventions required for the management of multidrug-resistant TB and HIV associated TB are also proving difficult.

In the context of newer interventions proposed under the new stop TB strategy<sup>4</sup> these challenges call for the generation of new information through effective research to answer questions how to maximally benefit from existing tools and interventions and secondly, around the feasibility, efficiency, and cost-effectiveness of the proposed newer interventions. Besides research into programme implementation, fundamental or basic research, to develop new tools—new vaccines, diagnostics and drugs to improve TB control interventions is equally essential at this point in the Global TB epidemic.

Research areas that could be fruitfully pursued to improve programme implementation are: (i) operational research into programmatic approaches to increase case finding and ensure access to quality treatment of all forms of TB, including smear negative, extra-pulmonary, pediatric, multi-drug resistant, and HIV associated TB, (ii) social, economic, and behavioral research that examines the larger domain of social and other determinants such as poverty, malnutrition, ethnic and gender differentials that affect the seeking and receiving of care for TB, and (iii) policy and health systems research that will provide insights into how TB control services are positioned and delivered through public health care systems and the means to strengthen the delivery of TB care, while at the same time, addressing some of the inherent constraints of these systems.

Another major area of research is therefore epidemiological research that examines the outcomes and impact of programme implementation and also helps to assess the cost-effectiveness of various interventions for TB control and their impact in turn, on overall health, social and economic development. Epidemiologic or evaluative research differs from operational research in that the outcomes could be specific to an individual country, region or project. However, an evaluation of the outcomes and impact does provide useful information to guide policy, strategies and plans in that setting. These evaluations also provide insights into processes that can be used to make these assessments in other settings.

Concurrent with research relating to programme implementation and evaluation as outlined above, basic research aimed at developing new tools is equally essential to achieving the long-term goal of TB control – TB elimination. It is basic research that will help develop newer more effective vaccines that would prevent progression from infection to disease, quicker, cheaper, robust, and yet more sensitive and specific diagnostics to diagnose all forms of TB including latent TB, and new less toxic drugs that would significantly shorten the duration of treatment with better outcomes and fewer chances of relapse.

While this paper draws on the deliberations and recommendations of the scientific working group of the UNICEF/ UNDP/ World Bank/ WHO Special Programme on Research and Training in Tropical Diseases (TDR) for priority research into TB control<sup>5</sup>, the research agenda proposed in this paper identifies the key research areas for TB control in the context of national TB programmes and health settings in the SEA Region.

Besides identifying research questions relevant to the three major areas described, this paper attempts to define priorities that could be considered as the most important to accelerate the programmatic management of tuberculosis in the South-East Asia Region over the next 5 to 10 years.

### **Research Priorities in TB 2008-2015: Aims**

The aims of undertaking research would be to ensure that cost-effective approaches and appropriate new tools are applied in countries in this Region towards improving TB control. Ideally, research performed should contribute to:

- Improving case detection, reducing diagnostic delays through improved access to better diagnostics
- Reducing individual morbidity and mortality and continuing TB transmission through effectively treating and curing all TB patients, including those with drug-resistance and HIV co-infection through a wide range of providers
- More accurately estimating the burden and impact of interventions on TB including MDR-TB and TB-HIV in countries in the Region, and applying this information to both guide strategies and interventions and better inform health policy, planning, financing for TB control
- Contributing to the development of new effective vaccines, simple, accurate, diagnostics and inexpensive, less toxic drugs that can shorten treatment regimens

## **2. RESEARCH INTO PROGRAMME IMPLEMENTATION**

### **2.1 Case finding**

The key questions to be addressed are where are the missing cases and how can case detection be improved? Case detection rates in the Region have slowly but steadily risen to the current 68% level among new smear-positive cases. However, this represents less than half of all TB patients, if TB patients with all forms of TB are taken into account, and not only those with smear-positive TB. Smear-negative, extra-pulmonary and particularly pediatric TB cases remain under diagnosed and if diagnosed, remain under-use or reported. In order for national programmes to increase case detection rates for all forms of TB, it would be essential first to identify barriers to patients access to diagnostic facilities, including transportation fees, work-related factors, gender discrimination second and most importantly the true availability of quality diagnostic facility at various levels within both public health systems and in the private sector and the quality and mechanisms of case reporting. Thirdly, there is also a need to improve case finding among hard-to-reach and neglected populations, i.e., people living in remote rural areas, urban slums, conflict or disaster areas, the homeless, orphans, migrants, workers in exploitive employment situations, drug users and prisoners. Appropriate alternative strategies to the ones being currently utilized, are therefore definitely required to reach services to all TB patients and to then have all cases diagnosed and notified. An understanding of the knowledge, attitude, social and behavioral practices of different population groups that lead them to seek or not seek care, and where, would form the basis of targeted messages for interventions to reach these population groups. For example, seminal research in the 1990s in India revealed that over 60% of TB patients sought care in the private sector<sup>6</sup>, leading to the development of approaches to involve private providers of various denominations. These approaches are now well established under the ambit of private-public mix DOTS, or PPM-DOTS by national programmes in the Region<sup>7</sup>. Reports from India, Indonesia and Myanmar now indicate that, where initiated, this private-public initiative has resulted in up to 25% increments in cases notified.<sup>8,9</sup>

### **2.2 Ensuring access and adherence to treatment**

The feasibility and cost-effectiveness of treating patients through the DOTS strategy in countries in the Region has been well documented<sup>10</sup>. However, ensuring access and adherence to treatment has been a difficult area, particularly, when large numbers of patients continue to seek treatment through private providers, large private sector hospitals, traditional healers, NGO clinics or under the health schemes of large public sector employers such as the Ministries of Railways, Defence, Mining, Agriculture etc., many of whom follow treatment regimens that are not in line with those of national programmes. Besides this, little has been documented on the magnitude, quality, performance and determinants that affect private providers' practices in the context of treating children, patients with suspected or confirmed drug resistance, or those co-infected with HIV. Research into approaches that could optimally involve this diverse group of providers to apply uniform treatment practices in line with DOTS and the International Standards of TB care, would go a long way, given their acceptance by the

community, flexible timings, and respect for confidentiality. This is particularly critical in the context of first and foremost, preventing the emergence of multi drug resistant TB (MDR TB), and in then extending treatment to those with MDR and possibly even XDR-TB.

In addition, an analysis of user fees even where services are ostensibly free need to be made to uncover any cost recovery schemes inbuilt within public health systems or applied by the providers themselves. If treatment involves frequent travel, long distances and transport costs, loss of earnings and neglect of house-hold responsibilities, approaches to reduce these indirect barriers that affect treatment adherence will need to be designed. Other provider and patient related factors, such as the time spent to counsel and motivate patients or the use of patient enablers or provider incentives, and the effect of these on adherences also need to be analyzed.

**Case Finding and Treatment Adherence: Some examples research questions:**

- What factors lead to delays in establishing a diagnosis of tuberculosis?
- How do user fees affect the seeking and accessing of care, and in turn, case detection, diagnosis and treatment?
- What community-based social research can enhance the identification of the most vulnerable subgroups and help define strategies to enable them to obtain quality TB care?
- What is the available data on implementation and outcomes of case-finding and treatment by other providers, outside of NTPs?
- What is the impact of DOT as opposed to other adherence support strategies (including. community-based support, frequency and duration of support interventions) on treatment outcomes?

### **2.3 Diagnosis**

Sputum-smear microscopy remains the cornerstone of the laboratory diagnosis of TB. However, it is well recognized that sputum-smear microscopy alone is inadequate for the diagnosis of a large majority of the 5 million prevalent cases of active TB in the Region, especially those with smear-negative, extra-pulmonary forms of TB, children with TB, and many of those co-infected with HIV. Diagnosing smear-negative and extra-pulmonary disease is dependant on more complex, and much more expensive modalities such as chest X-rays, mycobacterial cultures, pathology, other radiological and immunological tests. While mycobacterial cultures of sputum or other specimens remain the gold standard for the definitive diagnosis of TB, this approach entails delays in diagnosis. Most national TB control programmes lack efficient quality-assured laboratories that can reliably undertake culture and drug susceptibility testing for the

diagnosis of multidrug-resistant TB. Few national programmes in the Region may in fact, be able to fully support the use of culture or other modalities for the diagnosis of TB.

Other tests are often inconclusive due to a lack of sensitivity and specificity for active disease, and in addition, to cost concerns, can also be misleading in the presence of concurrent HIV infection. There is also a particular need to improve the diagnosis of pediatric TB. There are also a number of questions that need to be answered in the context of current algorithms to diagnose TB in children, smear-negative and extra-pulmonary TB in adults, and among PLHA against the backdrop of the differing prevalence of HIV in the different settings in the Region. Thus, particularly in the context of this Region, with the highest burden of TB, the absence of a simple, cheap and reliable point-of-care diagnostic test for all forms of active TB perpetuates under diagnosis or mis-diagnosis of a large number of TB cases.

### **Diagnosis: Some examples research questions**

#### **Laboratory Diagnosis:**

- What is the value and role of sputum processing and concentration (e.g. through use of bleach, centrifugation, sedimentation and combinations) in improving the accuracy and yield of smear microscopy?
- What is the role, feasibility, and applicability of newer diagnostics in routine field conditions?
- What is the impact of introducing the two-smear strategy in high-burden settings?
- What is the optimal use of mycobacterial culture systems, including automated systems, in TB diagnosis in resource-limited settings?

#### **Diagnostic algorithms:**

- What is the existing evidence base for the current diagnostic algorithms for TB diagnosis?
- What is the role of therapeutic antimicrobial trials in the diagnostic algorithms for smear-negative tuberculosis?

## **2.4 Clinical Management**

New elements of the Stop TB strategy include the management of MDR-TB, TB/HIV, and management of TB in special situations. While the management of these cases is built on the core principle of programmatic approaches, management of these cases also call for a focus on specific clinical aspects. Field level research to simplify treatment through adaptation of drug regimens, establish the optimal durations for treatment of HIV/TB and MDR-TB patients, and develop new strategies for treatment adherence among these patients being treated with more toxic combinations of anti-TB drugs, possibly even in combination with antiretroviral treatment, are critical as countries begin

to manage these cases. In the context of TB/HIV and MDR-TB, studies on the use of standardized versus individualized modalities for diagnosis, treatment and treatment follow-up, the most effective methods of supporting the adherence and validation of outcomes from these necessarily new modalities are essential. Similarly, the treatment of patients with other concomitant medical conditions such as pregnancy, diabetes, hepatitis, renal impairment, which necessitate defining optimal treatment regimens to avoid drug interactions, address issues of safety and toxicity and manage the immune reconstitution inflammatory syndrome (IRIS) are areas for clinical research.

### **Clinical management: Some examples research questions**

#### **Diagnosis of TB in PLHA**

- What is the optimal diagnostic test for detecting latent and active TB in persons with HIV infection, including smear negative and extra pulmonary TB?

#### **Diagnosis of MDR-TB**

- What is the optimal diagnostic algorithm for persons with suspected MDR-TB?
  
- Which rapid tests for drug resistance would be the most useful for national programmes to field test and consider for use?

#### **Treatment of TB-HIV co-infection**

- What is the optimal duration of treatment and adherence support strategies using existing regimens for TB in HIV-infected people?
  
- What are the optimal protocols for isoniazid preventive and co-trimoxazole in TB/HIV co-infection?

#### **Treatment of Multidrug resistant TB:**

- What are the optimal regimens and the duration and cost effective modalities for the treatment of the MDR TB in country specific situations?

#### **Treatment of TB in special situations**

- What is the safety and efficacy of current drug formulations in use for the treatment of children with TB?

## **2.5 Social, Economic, and Behavioural Research**

DOTS is a proven intervention for tuberculosis<sup>11</sup>. However, it is now recognized that DOTS has not been able to achieve the set targets as expected<sup>12</sup>, largely due to lower

levels of implementation than are necessary for the strategy to be fully effective. Besides health systems and programme related factors, social, economic and behavioral factors have played a significant role. Research into identifying the determinants of health seeking behavior, including gender differentials, which affect the uptake of available services, and exert an independent effect on the outcomes of programme implementation, are very relevant to the settings in the Region. The central focus of this kind of research would be identifying barriers that limit timely case detection and effective treatment in the context of poverty, other social inequities, and cost constraints, and in then identifying appropriate interventions that would mitigate these constraints.

There are a number of studies<sup>13, 14</sup> from countries from this Region on the economic losses at individual, family and national level on account of costs incurred by patients for TB treatment and diagnosis. Other studies have shown the disproportionate social impact on women and the young children, due to the coping strategies adopted by families. While the sex distribution of cases notified in the Region follows the recognized gender differential in the epidemiology of TB<sup>15</sup>, there is evidence that women often have less knowledge of TB and tend to accord a lesser priority to health seeking<sup>16</sup> besides being given lower decision making powers. At the same time, there are very encouraging examples of community-based approaches, deploying women to address these very same constraints<sup>17</sup>. A wealth of initiatives generated by NGOs particularly for case finding and treatment support, have increasingly been incorporated into routine service delivery by national programmes. These community studies have also revealed people's perceptions which have helped to design social and behavioral interventions to address these perceptions, resulting in decreasing the stigma towards tuberculosis in some communities<sup>18</sup>.

### **Social, Economic and Behavioral Factors: Some examples research questions**

- How can case-finding and case-holding be improved in the context of TB- and AIDS-related stigma?
- Do health care workers stigmatize patients and each other: How can this be overcome?
- What is the impact of current advocacy and communications strategies on changing behaviour—among patients, communities, providers and policy makers?

## **2.6 Health systems, Policy and Financing**

Both the strengths and the weaknesses of general health systems affect the way that national TB control programmes are able to deliver TB control services. Experience from countries is increasingly indicative of the difficulties in 'scaling up' of interventions in the face of poorly functioning health systems. How to address health system constraints in the context of TB control is a therefore a major area for research. These include a wide range of topics on access to health care, inequities in health service

delivery to different population groups, technical capacity within health systems, health planning, financing, management and priority setting. Studies on the economics of health service functioning and service delivery including cost-effectiveness studies, and modalities for sustainable cost-sharing also fall into this area of research.

Studies that supported the cost-effectiveness of DOTS undertaken in individual countries and by the World Bank<sup>19</sup> helped to both increase the uptake of the strategy in countries as well as to attract major funding for the expansion of DOTS Programmes in countries. Important insights have also been gained from studying health policy and health reform processes in countries in the Region that have undertaken major health sector reform. As a result of analyses of the impact of health sector reforms in Bangladesh, Indonesia and Thailand, steps have been taken by ministries of Health in these countries to redress elements that were perceived as adversely impacting TB control programmes. Health systems research can therefore contribute significantly to supporting evidence-based formulation of national policies to benefit service delivery. However, investments in health systems research in countries in this Region are as yet far from adequate to sufficiently influence policy formulation, and truly translate research into affordable interventions.

### **Health Systems, policy and financing: Some examples research questions**

- Where the gaps and what are the opportunities for effective delivery of TB control services within current health systems frameworks?
- How can available epidemiological data be more effectively used to guide health policy, priority setting and financing, to the greater benefit of TB control programmes? Does more data need to be generated in this context?
- What lessons could be learnt from current mechanisms and processes used for procurements, recruitment, financial disbursements etc within national health systems that could help guide health sector reform?
- How can health providers outside the public health sector, including private practitioners, NGOs and traditional healers, contribute to TB control?
- What is the optimum configuration of a national laboratory network? What is the role and models for improving private laboratories?
- What operations research studies (including mathematical and simulation models) could be used to determine resource needs, delivery sites, care models, costs and impacts of the delivery of TB services and TB/HIV collaborative activities?

### **3. EPIDEMIOLOGICAL RESEARCH: TRENDS, OUTCOMES AND IMPACT OF INTERVENTIONS**

It is estimated that nearly 40% of the 1.5 billion populations in the Region have been infected with tuberculosis (TB). At the same time, one-third of the world's TB cases or 4.8 million cases, are estimated to be in the South-East Asia Region. Five of the eleven countries in the Region are among the 22 countries globally with the highest burdens of TB. More TB cases are diagnosed among males than among females, the male: female ratio being 3:1. Though deaths due to TB have reduced after introduction of the DOTS strategy, the disease still claims more than 500,000 lives each year<sup>20</sup>.

Expanding HIV epidemics are being reported from Bangladesh, Nepal, Indonesia and in some states in India<sup>21</sup>. There is evidence that rising HIV prevalence is leading to a higher incidence and mortality from TB in areas, regions or among specific population groups most affected, but not to the same extent as has been observed in sub-Saharan Africa.

The magnitude of anti-TB drug-resistant TB is not well documented in the Region. From available survey data, the prevalence of multiple drug resistant TB (MDR-TB) among new cases in the Region ranges from 0.2 to 4.0 with a median of 2.0 percent. Among previously treated cases, the prevalence of MDR-TB ranges from 11.7 to 34.5 with a median of 16.5 per cent<sup>22</sup>. No representative data on the magnitude of drug resistance to second-line TB-drugs is as yet available from the region.

Although these numbers represent the results of epidemiological analysis based on actual notifications of cases detected, treated and reported to be dying and special studies including surveys of prevalence of infection and disease, and consensus between experts, the uncertainty surrounding the estimates of TB incidence, prevalence and mortality are large due to the variable quality of the underlying data. While information on smear-positive cases has become fairly reliable due to the recording and reporting systems in place under DOTS, many tuberculosis cases remain largely unreported. The calculation of TB incidence based on case notifications, the annual risk of infection surveys, and mathematical modeling using the Styblo principle<sup>23</sup>, are beset with imprecision for various reasons. This, therefore results in a number of questions around the denominator used to determine case detection rates in countries in the Region.

More accurate estimates of the TB burden can be obtained from prevalence surveys. Unfortunately, data from such surveys are limited in this Region, since these are time consuming and require a considerable investment. Besides this, it is also recognized that the incidence and prevalence of TB can vary widely within a country, due to a number of local factors that need to be analyzed to determine the epidemiological differences at sub-national level. Information on the actual numbers of people dying of TB is also lacking. India, Indonesia and Myanmar are among the countries that have undertaken TB mortality surveys.

More recently Bangladesh, India, Indonesia, Myanmar and Thailand have undertaken prevalence surveys. DPR Korea plans to hold ARTI survey to better estimate the disease burden. Bhutan plans to undertake a community based survey for tuberculosis in 2008.

### **Epidemiology: Some examples research questions**

- What are the most cost-effective survey methodologies to more accurately determine TB incidence, prevalence and mortality in the various countries in the Region?
- What new diagnostic tools can be used for identifying latent TB infection and conducting TB prevalence surveys?
- What is the impact of interventions so far on TB incidence, prevalence and mortality?
- What is the impact of other cofactors (tobacco, alcohol, diabetes) on the TB epidemic?
- What are the best measures to evaluate and what is the quality of data being reported through the routine recording and reporting systems in place?

## **4. FUNDAMENTAL OR BASIC RESEARCH**

### **4.1 Development of new Vaccines**

The Bacillus Calmette-Guerin (BCG) vaccine is currently the only vaccine in use against tuberculosis. The efficacy of this vaccine is limited to prevention of severe forms of tuberculosis among children. It has little or no effect on adult disease<sup>24</sup>. Recent progress in vaccine research has resulted in seven candidate vaccines in Phase I clinical trials.

The undertaking of vaccine trials require that local expertise be built in countries. Other prerequisites are accurate information on the local epidemiology of TB, existence of community programmes, coordination with national regulatory authorities and the national programme, local expertise in diagnostic procedures, immunological assays, and infrastructure for undertaking vaccine trials.

### **4.2 Development of new diagnostics**

Building on advances in mycobacterial genome sequencing and profiling, highly accurate but simple to use point-of service diagnostic tests are expected to become available within the next five years.

Several new diagnostic tests are in the pipeline at various stages of development. The Foundation for Innovative new Diagnostics (FIND), established in 2003, is a lead agency within the new TB diagnostics working group of the Stop TB Partnership. FIND is currently supporting the field-testing of rapid culture techniques in a number of developing countries, including in India. Given the burden of disease in countries in this Region, the field-testing of the new diagnostics such as the use of LED Microscopy, LAMP, simple nucleic acid amplification techniques etc. would contribute significantly to the body of knowledge that is required in order to routinely begin using these new diagnostics under national programmes.

### **4.3 Development of new drugs, including immune modulators**

Not only is TB a significant problem in South-East Asia but the Region has real capacity and potential to contribute locally and globally to the development, manufacturing and deployment of current and new drugs. Only a few pharmaceutical companies in the Region are involved in TB drug discovery and development. Major issues concerning the development of new tools include lack of facilitation of private sector involvement, with various groups working in a parallel unlinked manner, and a lack of dialogue between industry and national programmes. Moreover, the industry is often not involved at the ideation stage of product development or modification, proposed by national programmes. There is also limited access to technology transfer, particularly to small pharmaceutical companies in countries in this Region.

Besides development of new drugs, the primary challenge of identifying the best combination of individual drugs for clinical use remains. The high TB burden countries in the Region, could contribute significantly in determining the best regimens for use through clinical field trials, and to reducing the time lines for testing and deploying new regimens, in consultation with drug regulatory authorities

#### **New Tools Development: Some examples research questions**

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- How can programmes independently evaluate new diagnostics in field trials, including nucleic acid amplification, antigen, and antibody detection methods for diagnosis?
- Which vaccines trials could countries in the Region contribute to (vaccine trial design, efficacy)
- What support is required to evaluate new drugs and/or new combination regimens of novel TB drugs in countries of the Region?

## **5. CONCLUSIONS**

This is an opportune time for research in TB. Global investments in TB research have increased several folds. The odds today on significant returns on these investments is also greater than ever before, given that much more research can now be undertaken in countries of the world where the disease has the highest prevalence. However, firm and

more proactive links will need to be established between researchers and national TB control programmes in order to better address programmatic issues, and not biomedical advances alone. At the same time, capacity to undertake research will also need to be strengthened through attention to mandating institutions, training research staff, ensuring appropriate technology transfer and adequately financing research. Research institutions, both in the public and private sectors and national programmes in the Region must much more proactively engage in contributing to the development of new approaches and new tools for the diagnosis, treatment, and prevention of TB. In addition, while there is already a great deal of research information already available in countries, these need to be better documented in order to maximize their public health impact.

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