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An analysis of multi drug resistant tuberculosis control in Vietnam

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AN ANALYSIS OF MULTI DRUG RESISTANT TUBERCULOSIS CONTROL IN VIETNAM

By

HOANG THI THANH THUY

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Authorship

The work presented in this thesis was primarily completed by me, with support from my supervisors and colleagues. As a member of programmatic management of drug-resistant tuberculosis (PMDT) of Vietnam, I am able to access to the data, information from the National TB control Programme (NTP), and permissions required for this project. For most of my studies works, I used data collection from routine reporting and recording system of the NTP, the guidelines and SOPs issued by the WHO and the NTP. The coordination for my studies was majority based on the existing human resources and the NTP network from central to provincial and district levels. For the statistical analysis, I worked under considerable support from statisticians of Oxford University Clinical Unit (OUCRU) of Hanoi. During my PhD programme, I was extensively trained by OUCRU faculties and closely supervised by my supervisors, either in persons, through telephone, Skype or by email.

Publications

1. **Thuy Hoang Thi Thanh,** Sy Dinh Ngoc, Nhung Nguyen Viet, Hung Nguyen Van, Peter Horby, Frank GJ Cobelens and Heiman FL Wertheim. *A household survey on screening practices of household contacts of smear positive tuberculosis patients in Vietnam.* BMC Public Health 2014, **14**:713.
2. **Thuy Thi Thanh Hoang,** Nhung Viet Nguyen, Sy Ngoc Dinh, Hoa Binh Nguyen, Frank Cobelens, Guy Thwaites, Huong Thien Nguyen, Anh Thu Nguyen, Pamela Wright and Heiman F. L. Wertheim. *Challenges in detection and treatment of multidrug resistant tuberculosis patients in Vietnam.* BMC Public Health 2015, **15**:980.

Acknowledgement

Abbreviations

AIDS	Acquired Immune Deficiency Syndrome (AIDS)
ATP	Adenosine triphosphate
CHC	Commune Health Centers
CSF	Cerebrospinal fluid
CXR	Chest Xray
DHC	District Health Centers
DNA	Deoxyribonucleic acid
DOH	Department of Health
DOT	Direct observed treatment
DOTS	Directly observed treatment short course therapy
DRS	Drug resistance survey
DR-TB	Drug resistant tuberculosis
DST	Drugs susceptibility testing
DTU	District TB unit
EPTB	Extra pulmonary TB
ESBL	Extended-spectrum Beta-lactamases
EQA	External quality assurance
FGD	Focus group discussions
FLD	First line drug
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GLC	Green Light Committee
HIV	Human immunodeficiency virus
IGRAs	Interferon-gamma release assays
IMVS	Institute of Medical and Veterinary Science
KNCV	Royal Netherlands Tuberculosis Foundation
LED	Light-emitting diodes
LMIC	Low and middle income countries
LPA	Line probe assay
LTBI	Latent Tuberculosis Infection

MDGs	Millennium Development Goals
MDR-TB	Multi Drug Resistance Tuberculosis
MOH	Ministry of Health
MTB	Mycobacterium tuberculosis
NLH	National Lung Hospital
NTP	National TB control Programme
NT.71	National 71 hospital
NT 74	National 74 hospital
PAS	Para-Amino Salicylic Acid
PEPFAR	President's Emergency Plan for AIDS Relief
PF	Performance framework
PMDT	Programmatic Management of Drugs resistant Tuberculosis
PPV	Positive predictive value
RNA	Ribonucleic acid
SL DST	Second-line drug susceptibility testing
SLD.	Second line drug
SNA	Social network analysis
SOPs	Standard operational procedures
TST	Tuberculin skin test
TB	Tuberculosis
WHA	World Health Assembly
WHO	World Health Organization
WRD	WHO-approved rapid diagnostics
XDR-TB	Extensive drug resistant TB

Abstract

Multi-drug resistant tuberculosis is a major global health problem. Viet Nam is 14th among 27 MDR-TB high burden countries with an estimated about 5,100 MDR-TB cases among notified TB cases per year. Management of MDR-TB in Viet Nam is one of the main objectives of the TB control programme. This thesis provides an understanding of the current situation of MDR/XDR-TB in Vietnam and its control policies focusing on case finding strategy, targeting groups for MDR-TB screening. MDR-TB contacts, one of the high risk groups recommended by the WHO is a focus of this thesis. The thesis presents screening practices of household contacts of TB patients, feasibility of TB contact investigations, and to identify challenges and solutions for a successful implementation of an efficient contact investigation among MDR-TB patients in Viet Nam.

Since 2009, the programmatic management of drug resistant tuberculosis (PMDT) was piloted in Viet Nam following the development of 2009 country MDR TB guideline. A year after the WHO updated guideline was disseminated, the country revised its guideline and SOP to be in line with WHO's recommendations and contextualized to local capacity and resources. The PMDT has been rolled out and scaled up in the country. However, lack of resources, limited communication on policy changes to lower level, unable to provide screening to all risk groups, inadequate capacity to perform diagnosis of mono and poly resistant TB and second-line DST have posed significant challenges for the NTP to implement their policy.

This study found that only about 30 % MDR TB cases was detected through the PMDT system. The possible reasons we identified were: (1) delay in fully rolling out PMDT policies and limited capacity of the system, mostly due to inadequate resources, (2) operational factors, and (3) neglecting high risk groups during MDR-TB screening, particularly close contacts of MDR TB patients. Noteworthy, the NTP strategy relies on "passive case finding" while the proportion of household contacts of smear-positive tuberculosis patients screened for TB under the current passive screening approach of the Vietnam National TB program is very low compared with prevalence of TB among contacts in high burden countries, particularly for contacts under 5 years of age. Although screening of close contacts of MDR-TB patients is recommended by the NTP of Viet Nam, this is generally not done. Therefore, a different

approach is needed. This study applied Social network Analysis (SNA), which is a more comprehensive approach than traditional contact tracing. However, with SNA of 99 MDR-TB index patients we were not able to detect new MDR-TB cases. The fact we found no new MDR-TB cases may be explained by reduced fitness of MDR-TB and the short follow up time of our study of 6 months.

The results of this study suggest that there are several interventions that could improve the PMDT program in Viet Nam. Firstly, the National TB control Program should standardize and decentralize training on PMDT and provide staff with updated information on policy changes through proper communication channels. Capacity on MDR-TB diagnosis and treatment should be strengthened. PMDT should expand ambulatory care of MDR-TB treatment and expand risk group for MDR-TB screening. MDR TB case finding could be strengthened by provision of information and education of close contacts of MDR-TB patients, with special attention to children; and to perform more research on how active contact investigations should be done for MD-TB to have the best yield. The NTP should allocate more resources to MDR-TB control, particularly well-trained staff.

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Chapter 1. INTRODUCTION

1.1 What is tuberculosis?

Tuberculosis (TB) is an infectious disease caused by closely related acid-fast bacteria known as the *Mycobacterium tuberculosis* complex (MTB) [1]. The causative agent of tuberculosis was discovered by the Nobel laureate Robert Koch who published on it in 1882[2]. The most common MTB pathogens that cause human disease are *M. tuberculosis* and *M. africanum*[3]. TB can occur in any part of the body, but occurs mainly in the lungs in 90% of the symptomatic cases (pulmonary TB). After inhalation, the bacteria cause a primary infection in the lungs, from which the bacteria disseminate to other organs through hematogenous spread[4-6]. Following a primary infection, most adults (90-95%) do not develop disease when infected with *M. tuberculosis*, this is known as latent TB infection (LTBI)[7]. Approximately 5-10% of adults infected with MTB develop symptomatic or active TB[7][8], most commonly in the first two years after infection [4][6] (Figure 1-1).However, the risk of tuberculosis development may vary among different settings[9]. There is an increased risk of developing TB in immune compromised individuals, including but not limited to: people infected with human immunodeficiency virus (HIV)[10-12], the very young or elderly [13], poor nutrition status [14], diabetes[6][15], alcoholics[16], and use of immunosuppressive drugs [5][17]. LTBI can become active TB (reactivation) in patients with immunosuppression[8].

TB bacilli are transmitted through the air as they are expelled into the air in small airborne droplets (0.5 to 5.0 μm in diameter) by pulmonary TB patients when they cough or sneeze and subsequently inhaled by close contacts (Figure 1-1).Individuals with close contact to pulmonary TB patients, for instance family members, are at risk of infection with MTB, depending on duration of exposure and density of bacilli in the air[6][18]. Patients with LTBI do not transmit infection. As mentioned earlier, TB usually involves the lungs, however, other organs may be involved in extrapulmonary TB (EPTB). EPTB is more common in HIV patients[5][19] and in infants[20], and accounts for 50% to 60% of all TB among patients with *Acquired Immune Deficiency Syndrome* (AIDS)[5][21].

Figure 1-1. Phases of tuberculosis infection: Latent TB infection and active TB
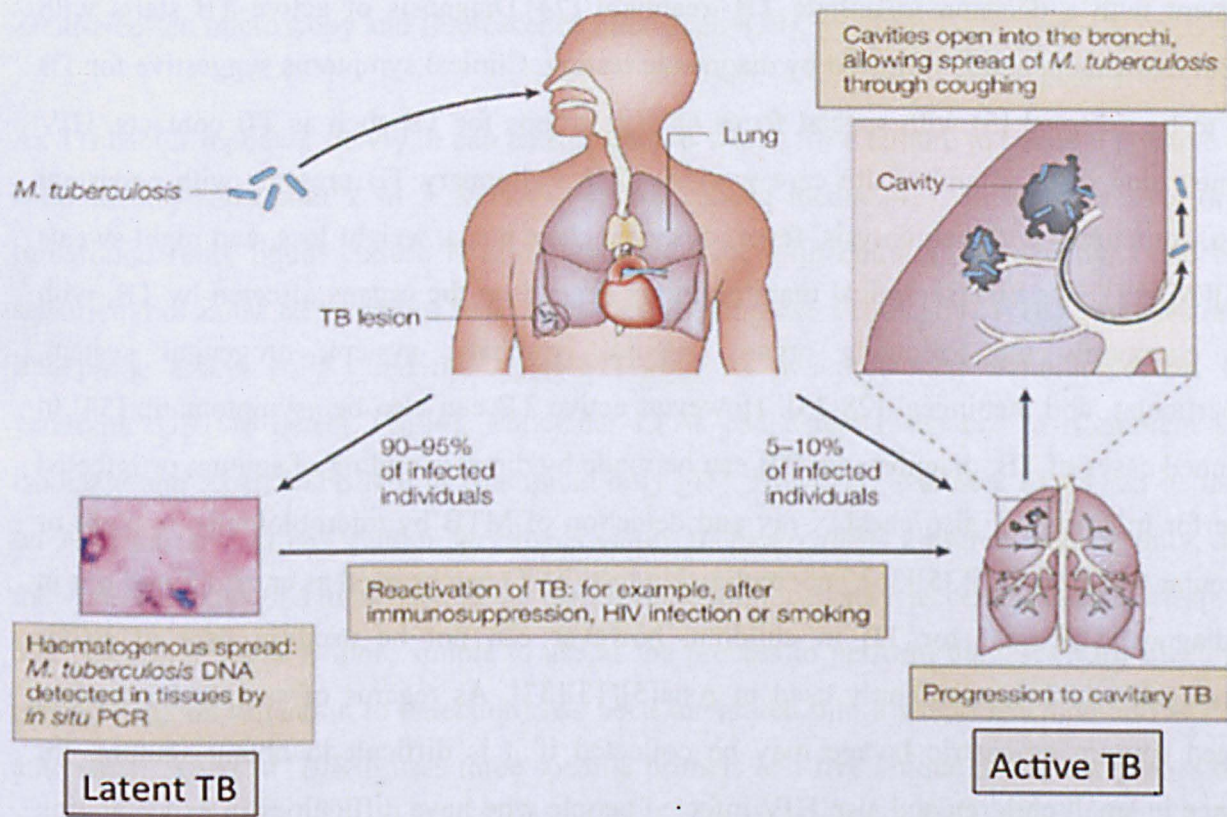
TB is airborne and can establish primary infection in the lung. Hematogeneous spread may occur approximately three weeks after unimmunized individuals are first infected with detectable DNA of MTB in various organs. In about 90%-95% of individuals, the infection remains latent (LTBI) and remains latent for decades. LTBI can be reactivated when an individual is immunosuppressed, particularly through infection with HIV. [22]

1.2 How is TB diagnosed?

Diagnosis of TB depends on whether we are dealing with latent or active TB, and in case of active TB, which organs are affected. Below I briefly summarize the diagnosis of TB for the different circumstances.

1.2.1 Active TB

TB is a clinical syndrome that can be identified either by bacteriologically confirmed and/or based on clinical criteria only [23][24]. A bacteriologically confirmed TB case is diagnosed by

positive result in smear microscopy examination, culture or World Health Organization (WHO)-approved rapid diagnostics (WRD). Clinically diagnosed TB is based on clinical judgment with a decision to initiate TB treatment [24].Diagnosis of active TB starts with clinical assessment and is followed by diagnostic testing. Clinical symptoms suggestive for TB need to be assessed [5] with special focus on risk groups for TB such as TB contacts, HIV patients, lung disease, and health care workers [25]. Pulmonary TB presents with persistent cough, sometimes with hemoptysis, fever, dyspnea, chest pains, weight loss, and night sweats [4][5][26][27]. For EPTB, clinical manifestations depend on the organs affected by TB, with most commonly the following organs: pleura, lymphatic system, urogenital system, osteoarticular, and meningeal [28-33]. However, active TB can also be asymptomatic [34].In presumed cases of TB, diagnosis for TB can be made by direct sampling of sputum or infected tissue for microscopy, also chest X-ray and detection of MTB by microbiological culture or molecular techniques[5][35][36].Tuberculin skin test (TST) can be used as an additional test in the diagnostic process for TB in children, however can not be used in case of BCG-vaccination, which is commonly used in Asia[5][13][37]. As regards of sample for testing, induced sputum or gastric lavage may be collected if it is difficult to obtain sputum, for instance in small children and also HIV infected people who have difficulties in expectorating sputum [13].

To diagnose pulmonary TB, microscopic examination of a sputum smear following a staining procedure in which the TB bacilli retain the color of the stain after an acid wash, is performed. TB bacilli are therefore also referred to as acid-fast bacilli (AFB; Figure 1-2). This staining procedure is called a Ziehl-Neelsen stain. Among people presumed to have TB this has been the basic diagnostic test for TB worldwide. Microscopy has a limited sensitivity by the threshold of detection, which is 5,000 – 10,000 bacilli per milliliter of sputum[38]. The sensitivity of the sputum smear ranges from 20% to 80% in adults with pulmonary TB [39][40].

Also fluorescent staining methods like auramine can be used to detect mycobacteria in samples[39][41]. Conventional fluorescence microscopy takes less time and is more sensitive than Ziehl-Neelsen. However, it is more costly. Less expensive light-emitting diodes (LED) have developed and are recommended by the WHO to replace conventional fluorescence microscopy and can be easily implemented and used in resource-limited settings. LED

microscopy increases sensitivity by approximately 5% compared toZiehl-Neelsen and conventional fluorescence microscopy[39]. LED has equal specificity compared to direct Ziehl-Neelsen microscopy and fluorescence microscopy[39].

As TB bacilli replicate slowly, it can take up to 4–6 weeks for a culture to become positive on solid media, and about 2 to 3 weeks in liquid culture media [42]. In addition to shorter turnaround time, liquid culture is more sensitive than solid culture[43].Recently, rapid and sensitive molecular technologies have been used to diagnose TB. So far, WHO endorses only line probe assays (LPA) and the Xpert MTB/RIF as two molecular technologies for the genotypic DST to detect TB[44]. Molecular LPAs can detect resistance to rifampicin and isoniazid and Xpert MTB/RIF to rifampicin only [45]. However, available LPAs can be used on AFB smear-positive sputum specimens or on *M. tuberculosis* cultured isolates only, and they are recommended to be used at the high level laboratories such as central laboratories[44]. The Xpert MTB/RIF is more simple to use as the process to perform the test (from specimen preparation, amplification to detection) has been integrated into a single machine and is fully automated. Xpert MTB/RIF uses three specific primers and five unique molecular probes that can both detect TB specific Deoxyribonucleic acid(DNA) and rifampicin resistance (see below). In 2013, WHO recommended Xpert MTB/RIF to be used as a replacement test for smear microscopy and can be used to support diagnosis of TB in children and HIV infected people. For replacement of conventional microscopy to be the initial diagnostic test for TB, Xpert MTB/RIF has a pooled sensitivity of 88% and a pooled specificity of 99%[46].

For presumed cases of EPTB, also Xpert MTB/RIF [46] or sputum smear, TB culture and chest X-ray are used. Additional samples are collected depending on the location of EPTB. For example, cerebrospinal fluid (CSF) will be collected in case of presumed TB meningitis or pleural fluid in case of possible pleural TB [36]. In2013, the WHO advised to use the Xpert MTB/RIF test in preference to conventional diagnostics in case of testing cerebrospinal fluid; however the use of Xpert MTB/RIF for pleural fluid is currently not recommended [46].

Figure 1-2. Acid-fast bacilli in sputum smear

(source:http://phil.cdc.gov/PHIL_Images/20040615/d094324845a24eb3a7bfe0d1f8e4a637/5_1
ores.jpg)
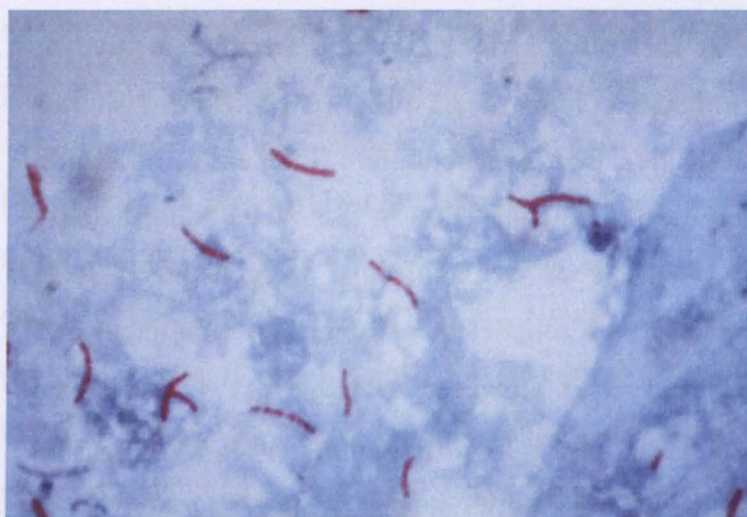
1.2.2 Latent tuberculosis infection (LTBI)

In LTBI, the bacillus is generally not directly detected. Therefore, diagnosis of latent TB depends on the existence of a TB specific host response test[8]. Available immunological tests for LTBI include: tuberculin skin test (TST) and interferon-gamma release assays (IGRAs)as well as other measures of host response [5][36]. These tests, however, cannot differentiate LTBI from tuberculosis disease. Therefore, active TB needs to be excluded, whereby all diagnostic tests should be negative. The diagnosis LTBI becomes more likely with a positive immune response and a history of a TB contact. Depending on the country specific resources, the priority to systematically test for LTBI among risk groups who are more likely t(o develop active TB need to be considered [8].

1.2.3 Drug resistance testing

The TB bacilli can become resistant to one or more anti-TB drugs used. If it is resistant to at least isoniazid and rifampicin, the two most powerful anti-TB drugs, it is classified as multidrug-resistant tuberculosis (MDR-TB). In case of MDR-TB plus additional resistance to any fluoroquinolone, and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), it is defined as extensive drug resistant TB (XDR-TB). Drug resistance can emerge and spread due to poor treatment of TB and due to transmission to

people who are in contact with MDR-TB patients [44]. Drug susceptibility testing (DST) of TB is an important aspect of TB management.

DST indicating the sensitivity of the strain to anti TB drugs can be performed by either phenotypic or genotypic methods. Phenotypic methods are based on growing bacilli in the presence of anti-TB agents[35][44]. Phenotypic methods can detect drug resistance without considering the molecular mechanism of drug resistance. It can be performed in liquid or on solid media by direct or indirect methods. The direct test deals with the specimen while indirect test uses a strain already isolated from a specimen[44]. Conventional phenotypic DST on solid or liquid culture has been used to detect susceptibility to first and second line anti TB drugs.

Different from phenotypic methods, genotypic DST detects genetic mutations related to resistance to specific TB drugs. Recently, rapid tests (LPA to detect rifampicin and isoniazid resistance; Xpert MTB/RIF to detect rifampicin resistance) have become available. The sensitivity and specificity of Xpert MTB/RIF is 95% and 98%, respectively when it is used to detect rifampicin resistance[46]. As not all genetic mutations conferring resistance are known, molecular techniques have their limitations. Currently, phenotypic DST techniques are recommended to detect second line drug(SLD) resistance. Molecular tests for fluoroquinolones and second line injectable drugs are available and in accordance with WHO guidance can be used as a rule-in test for treatment regimens specifically designed to deal with MDR TB with additional resistance to SLD. However, genotypic SLD DST is not yet endorsed by WHO as a replacement for phenotypic SL DST[44].

1.3. Treatment of tuberculosis

1.3.1 Treatment of LTBI

Preventive therapy for LTBI aims to prevent people with latent TB infection from development of active TB (reactivation). There are several LTBI treatment options: 6-9 months isoniazid, 3–4 months isoniazid with rifampicin, 3 months isoniazid and rifapentene,and 3–4 months rifampicin alone [8]. These treatment options are **not** recommended for those who have been in close contact with MDR-TB due to risk of resistance. There is controversy about whether preventive therapy should be provided to close contacts of MDR-TB and which drugs should be used. So far the experience and evidence of treatment for LTBI in contacts of MDR-TB is

limited and it is not recommended to routinely treat them with second-line anti-TB drugs at this time [44].

As regards of LTBI treatment in close contacts of MDR-TB patients, currently there are two systematic reviews that analyzed the use of second line anti TB drugs in MDR-TB contacts to prevent disease development. The reviews used data from January 2004 to April 2011and included 19 references and 3 studies with a total of 1195 patients. One study in the reviews showed that no TB developed either from contacts who were treated or the untreated with prophylaxis, while other two studies reported non-significant risk differences of developing active TB disease (4% ; 95%CI: −3 to 12, and 5%; 95%CI: −2 to 11). In addition, evidence from these three studies was considered as low quality due to limitations in study design, inconsistencies among the results and methodology. The evidence from the reviews therefore is not sufficient to decide whether or not to apply preventive treatment for contacts of MDR-TB and warrant more research, preferably clinical trials[47]. A more recent prospective observational study in Micronesia showed that no contacts of MDR-TB patients who received preventive treatment with a fluoroquinolone developed MDR-TB disease, while 3 of 15 contacts who did not receive prophylaxis developed MDR-TB disease[48].

1.3.2   Treatment of TB

TB is treated by taking a combination of different drugs with multiple targets (figures 1-3 and 1.4). This should prevent monotherapy reduce the likelihood of spontaneous mutations arising and thus emergence and amplification of drug resistance. According to the WHO, standardized treatment regimens are designed for different patients groups including (i) new patients who are supposed or known to be susceptible TB, (ii) previously treated TB patients and (iii) multi-drug resistant TB patients (MDR-TB). There are 5 groups of anti-TB drugs recommended by the WHO for treatment of TB [23] (table 1-1).

Table 1-1.WHO categorization of anti-tuberculosis drugs.

Group 1	First-line oral drugs	Rifampicine (R), isoniazid (H), pyrazinamide (Z), ethambutol (E), Rifabutin(Rfb), Rifapentine (Rpt)
Group 2	Injectables	Streptomycin (S), Kanamycin (Km), Amikacin(Am), capreomycin (Cm)
Group 3	Fluoroquinolones	Levofloxacin (Lfx), moxifloxacin (Mfx), gatifloxacin (Gfx)
Group 4	Oral bacteriostatic drugs	Pro/ethionamide (Pto, Eto), cycloserine (Cs), terizidone (Trd), Para-aminosalicylic acid (PAS),Para-aminosalicylate sodium (PAS-Na)
Group 5	Drugs with limited data on efficacy and/or long term safety in TB treatment	Bedaquiline (Bdq), Delamanid (Dlm), linezolid (Lzd) , Clofazimine (Cfz), amoxicillin/clavulanate (Amx/Clv), Imipenem/cilastatin (Ipm/Cln), Meropenem (Mpm),High-dose isoniazid, Thioacetazone(T), clarithromycin (Clr),

Treatment for new TB patients (drug susceptible cases)

New pulmonary TB patients are recommended to receive a six-month regimen containing rifampicin: 2HRZE/4HR (see Table 1-1 for guide to which letter corresponds to what drug; the numbers refer to duration in months. Brackets around a combination of drugs indicates the drug is combined in a fixed dose combination tablet. The figure behind a drug indicates the number of weekly doses, if the drug is not taken daily). The optimal dosing frequency is daily throughout the treatment course. However, intermittent frequency (three times per week) of 2HRZE/4(HR)3 or 2(HRZE)3/4(HR)3 may be provided if direct observed treatment (DOT) is ensured, the patient is negative for HIV or not living in an HIV prevalent setting [23]. Isoniazid, rifampin, ethambutol, and pyrazinamide are used for two months during the intensive phase, followed by isoniazid and rifampin for four months during the continuation

phase (Table 1-2). In settings with high levels of isoniazid resistance, ethambutol is recommended to add to continuation phase to prevent possible monotherapy of rifampicin [23].

Table 1-2. Standardized regiment for TB treatment for new and previously treated cases[23].

(See Table 1-1 for guide to which letter corresponds to what drug)

Category	Intensive phase	Continuation phase
New patients	2 HRZE	4 HR, or 4 HRE (if high levels of isoniazid resistance)
Previously treated patients (Medium or low risk of MDR-TB, conventional DST is used)	2HRZES/1HRZE	5HRE
Previously treated patients (High risk of MDR-TB, conventional DST is used)	Empirical MDR regimen to be revised based on DST results	

Treatment for previously treated TB patients

Previous TB treatment may suggest possible drug resistance[49]. Therefore, these patients should be tested by DST to at least isoniazid and rifampicin before the start of treatment to detect drug resistance and revise the regimen accordingly. If rapid DST is available, the results should be used to guide treatment. For settings that use non or conventional DST only, treatment with second line anti TB drugs is recommended for high risk patient for MDR-TB (treatment failure cases), and the so called retreatment regimen is started with first line drug regimen (2HRZES/1HRE/5HRE) for medium or low risk group patients (relapse and treatment after lost to follow up cases, table 1-2)[23]

Treatment of extrapulmonary TB

EPTB and pulmonary TB can be treated with the same regimens[23]. However, for TB meningitis, it is recommended to extend the treatment to 9–12 months [50][51] and streptomycin should be used instead of ethambutol. For bone or joint TB a 9-months treatment duration is recommended [51]. Corticosteroids are recommended to use as adjuvant therapy for TB meningitis and pericarditis [52][53].

Figure 1-3. First line treatment for drug susceptible TB.

(source:https://www.niaid.nih.gov/topics/tuberculosis/Understanding/WhatIsTB/ScientificIllust rations/pages/firstlineillustration.aspx)
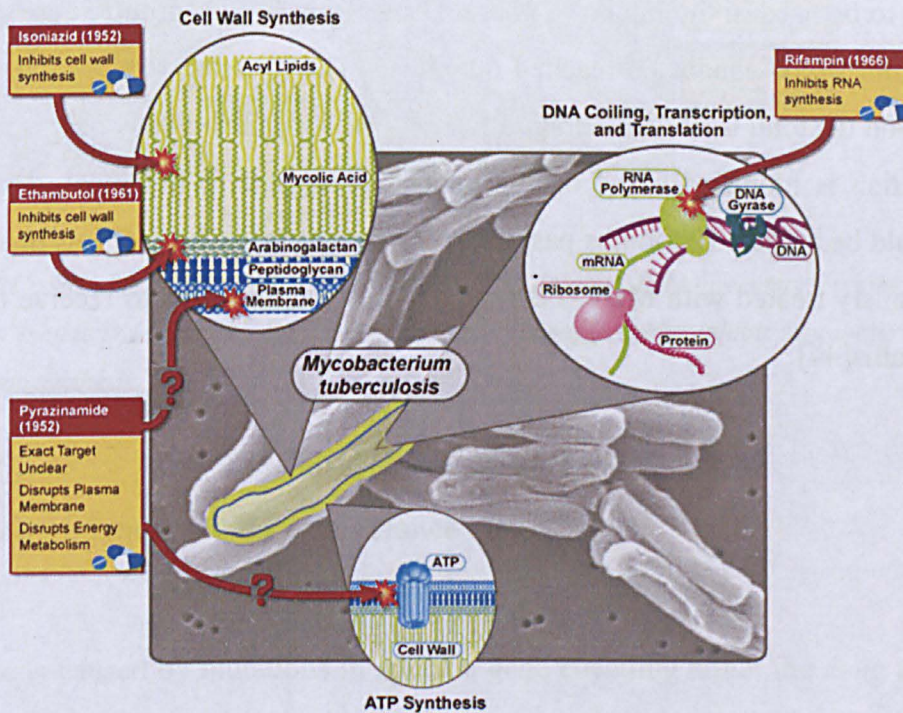
Treatment of multi-drug resistance TB

According to the WHO[44], there are 2 types of treatment regimes for MDR-TB patients including (i) standardized treatment based on regional resistance data whereby all patients in a defined patient group receive the same regimen designed based on drug resistance survey information, (ii) individualized treatment designed based on the individual patient's previous

TB treatment history and DST results. Standardized regimens are recommended over individualized regimens due to unavailability or unreliability of DST results for specific drugs in most countries and the long turnaround time for culture based DST. The combinations of these two designs may be used. There are four principles to the design of MDR-TB treatment:

(i)   use at least four drugs certain to be effective;

(ii)   prevent the use of drugs with potential for cross-resistance;

(iii)   do not use toxic drugs;

(iv)   use the most potent drugs

The combination of effective drugs with different targets is preferred (Figure 1-4). Choosing a second line injectable agent is the first step in building the regimen. Pyrazinamide is recommended to be used in the intensive phase. Drugs from WHO 'group 5' are only added if the target of four drugs cannot be reached otherwise. The duration of the intensive phase is eight months and the total treatment duration is 20 months for most newly diagnosed MDR-TB patients. Duration is modified based on the patient's response to treatment. Total length of treatment should be at least 12 months past the culture conversion, but not less than 20 months. Patients previously treated with MDR-TB regimen are recommended to receive treatment for at least 24 months[44].

Figure 1-4. Possible Effective Treatments for MDR-TB

(source:https://www.niaid.nih.gov/topics/tuberculosis/Understanding/WhatIsTB/ScientificIllust rations/pages/multidrugresistantillustration.aspx)
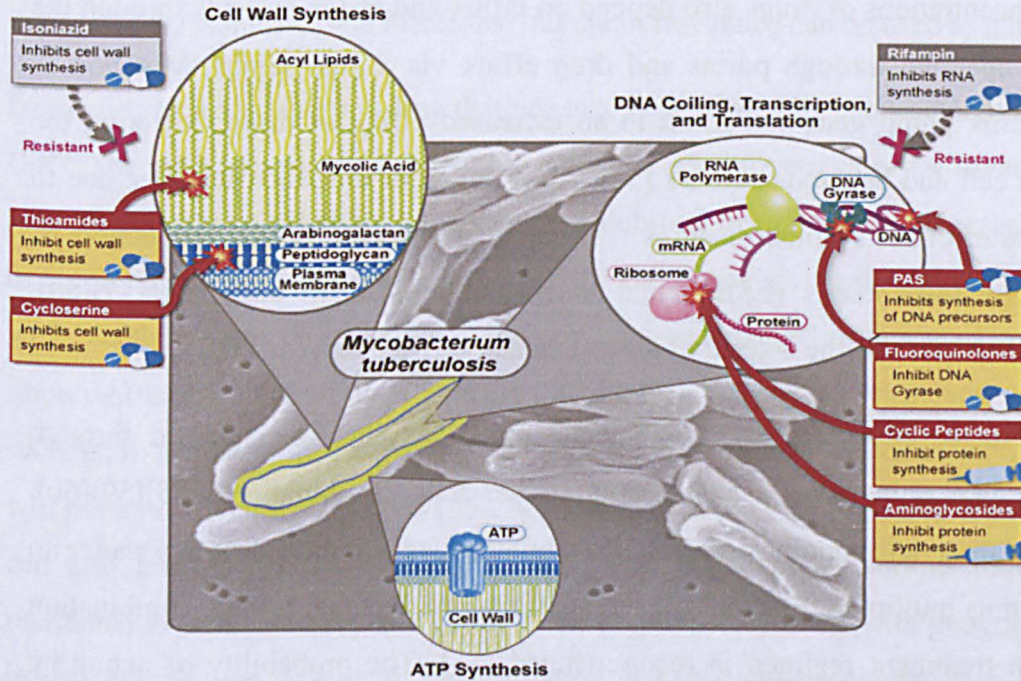
Thioamides, and Cycloserine inhibit cell wall synthesis. PAS inhibits DNA precursors synthesis; Fluoroquinolones inhibit DNA gyrase; Cyclic Peptides and Aminoglycosides inhibit Mycobaterium tuberculosis protein synthesis.

1.4 Drug targets and mechanisms of resistance

Background

Drug resistance is caused by mutations in specific gene encoding either the *drug target* or the *enzymes* involved in drug activation[54][55]. These mutations may occur by mutations, insertions or deletions of nucleotides of specific genes resulting in modification of drug target, block pro-drug activating enzyme, or destroy drug action by increasing the targeted gene products [54][55]. Resistance may also involve decreases in permeability and/or increase in efflux leading to decrease in drug accumulation[55][56].

There are two types of drug resistance distinguished including intrinsic resistance and acquired resistance. Intrinsic drug resistance concerns the natural characteristics of the MTB making it

resistant to many kinds of antimicrobial agents. *M. tuberculosis* bacilli have a lipid rich cell wall with a low permeability limiting uptake of small molecule, particularly hydrophilic, drugs into the cell. But passive diffusion is only partly responsible for uptake of drugs by the cell. The intracellular concentrations of drugs also depend on influx and efflux systems through the cell wall. Influx is operated through porins and drug efflux via efflux pumps. Mutation in regulators of the efflux pump gene can result in an increased efflux of drugs, lowering the concentration in the cell and hence its activity [56]. An example of intrinsic resistance due to efflux pumps is tetracycline. Another natural resistance mechanism is the production of extended-spectrum Beta-lactamases (ESBL) that inactivate beta-lactam antibiotics[57][58]. Intrinsic resistance greatly limits the arsenal of drugs that can be used to treat TB.

Acquired drug resistance is caused by spontaneous mutations that are selected through incorrect treatment, like only using a single drug, rather than combinations [55][59][60]. Treatment for TB with serial monotherapy may lead to stepwise acquired drug resistance to different drugs and thus multiple drug-resistance TB (MDR-TB). For that reason, combination of anti-TB drugs in treatment regimen is recommended [55]. The probability of acquiring resistance from spontaneous mutations varies between first line anti-TB drugs from 10^{-8} to 10^{-6}[61].Mutation rates can vary between different lineages [62][63]. The risk of a resistance mutations is decreased if multiple drugs are used together as it reduces the probability of selecting for resistance to below 10^{-18} per cell division [55].

Resistant mycobacteria can subsequently be transmitted to other hosts and cause primary resistance [60]. The transmission of MDR-TB strain from MDR-TB patients to their contacts can drive MDR-TB epidemic. Over time, selected resistance strains can replace the population of susceptible TB strains due to selective pressure from treatment[64]. Diagnosis and treatment delay, or less effective treatment of MDR-TB increase transmission of TB strains due to a prolonged infectious period [65][66].

Below follows a brief description of key resistance mechanisms of TB drugs.

Rifampicin: Rifampicin is a bactericidal drug and considered together with isoniazid to be the basis of short-course TB treatment. Rifampicin 'kills' the TB cell by inhibiting protein synthesis [44][55][67]. The target of rifampicin is the beta-sub unit of ribonucleic acid (RNA)

polymerase encoded by gene *rpoB*. Mutations in this gene can lead to changes in the structure of RNA polymerase, consequently leading to the decrease in drug affinity for its target and development of resistance[55][60]. Most rifampicin resistant strains are also resistant to other drugs, mainly isoniazid, and therefore rifampicin resistance can be used as a marker for MDR.

Isoniazid: Isoniazid is a pro-drug that needs to be activated by catalase/peroxidase, encoded by *katG*. The most important targets of the activated drug are enzymes for mycolic acid synthesis (enoyl reductase encoded by *inhA*), thereby inhibiting mycolic acid synthesis, a key component of the MTB cell wall. Several mutations in the katG gene giving rise to resistance may interfere with catalase/peroxidase activity thereby compromising virulence. However, the most important katG mutation at 315 doesn't affect this activity nor virulence, which is why it is successful. Mutation in *KatG* can result in a loss of catalase/peroxidase activity and isoniazid will not be sufficiently activated [55]. Mutations in *inhA* or its promotor region and other genes can also lead to isoniazid resistance [68]. The frequency of various mutations conferring resistance to isoniazid vary according to the genotypes of MTB with geographical differences in their distribution as a result [69].Mutation in *KatG* was considered to be more frequent in resistant strains [70] and associated with high-level resistance to Isoniazid, while mutation in inhA is likely associated with low level resistance to isoniazid[71][72]. Isoniazid resistance is considered at low level when there was >1% growth of MTB in the presence of 0.2 µg/mL of INH. High level Isoniazid resistance is classified when there is >1% growth of MTB in the presence of 1 µg/mL of INH. In addition to the most common mutations in kat G and inhA, mutation in many other genes are associated with INH resistance such as *ahpC, kasA* and NDH[55][72].

Pyrazinamide: Pyrazinamide is a pro-drug that activated by the enzyme pyrazinamidase/nicotinamidase coded by the *pncA*. The pro-drug passively diffuses into the MTB cell where it is converted to the active metabolite pyrazinoic acid[72]. This drug is most effective during the early stage of therapy before inflammation has subsided and is able to kill dormant mycobacteria[73]. The target of this drug is not fully clear. The possible mode of action of pyrazinamide involves the role of pyrazinoic acid to inhibit membrane transport. This causes inefficient efflux pump whereby pyrazinoic acid would be accumulated inside and kill the cell[72]. It possibly includes inhibition of mycobaterial fatty acid synthetase enzyme in

replicating bacilli[74], and disruption of Adenosine triphosphate (ATP) synthesis[75] interfering with the function of a ribosomal protein[76]. Several point mutations in the 600 base-pair *pncA* gene may lead to pyrazinamide resistance[77]. Alternative resistance mechanism of this agent includes defects in transportation of the agent into the MTB cell due to changes in porins[78].

Ethambutol: This drug inhibits enzyme arabinosyl transferase, which helps to synthesize the major cell wall polysaccharide arabinogalactan. Resistance to this agent is a multi step process involving genes in the *embA*, *embB* and *embC* cluster. There is evidence that mutations in codon 306 of the *embB* gene leads to resistance to ethambutol. This mutation also predisposes the MTB cell to develop resistance to several other drugs, thereby generating multidrug resistant strains [79].

Streptomycin: The mode of action of this aminoglycoside drug is to inhibit ribosomal protein S12 and thereby inhibiting protein synthesis. It was the first drug to be used in TB treatment and initially used as monotherapy, resulting in high resistance levels to this drug. Resistance is determined by mutation in the *rrs* and *rpsL* gene resulting in alterations in the streptomycin binding site[55].

Fluoroquinolones: The target of this drug is DNA gyrase, encoded by the genes *gyrA* and *gyrB*. DNA gyrase catalyzes the supercoiling of DNA and is essential for efficient DNA replication, transcription, and recombination. Fluoroquinolones can bind to DNA gyrase and inhibit its activity with cell death as a result [55][60][72]. Mutations in these genes cause changes in DNA gyrase, and fluoroquinolone is unable to bind to this target.

Second line injectables: The second line injectable drugs commonly used to treat MDR-TB are kanamycin, amikacin that belong to aminoglycoside antibiotics and capreomycin that belong to cyclic peptide antibiotics. The targets of kanamycin and amikacin are the enzymes 16 rRNA (encoded by gene *rrs*) and aminoglycosidase acetyltransferase (encoded by gene *eis*) [55][60][64]. Targets of capreomycin are the enzymes:16S rRNA encoded by *rrs* gene and rRNA-methyltransferase encoded by *tlyA*[55][60][64]. These enzymes catalyze protein synthesis. Kanamycin, amikacin and capreomycin attack its targets to inhibit protein synthesis

and kill the cell. Mutations in these genes change its product (enzymes) and as a result are not recognized by second line injectable drugs to be inhibited. Cross-resistance between kanamycin and amikacin has been reported [80][81]. However, they are not considered to be fully cross resistant [82].

Cycloserine: The target of this drug is not exactly defined. Cycloserine can block the activity of D-alanine to inhibit the peptidoglycan synthesis[72]. In addition, it can interfere the process to convert from L-alanine to D-alanine by inhibition of D-alanine racemase (*AlrA*)[83]. Some studies showed that resistance to cylcoserine is caused by overexpression of *alrA*[84] or mutation in gene *cycA* encoding for the D-alanine transporter[85].

Para-Amino Salicylic Acid (PAS): Thus far the target of this drug is not clearly defined [72]. It supposedly interferes with folate synthesis. One study showed that mutations in the *thyA* gene[86], another study identified mutations in *folC* related with PAS resistance [87]. However, other mechanism may result in resistance to PAS since only less than 40% of resistant strains had mutations in *thyA*[88].

Ethionamide: Ethionamide is a pro-drug that is activated by monooxygenase[72]. This enzyme is encoded by the *ethA* gene which is regulated by transcriptional repressor encoded by the *EthR* gene. When activated, it inhibits the enoyl-ACP reductase enzyme and interfere the mycolic acid synthesis to kill the cell [89]. Mutations in *etaA/ethA, ethR* and *inhA* genes cause ethionamide cannot be activated, with ethionamide resistance as a result[90].

Clofazimine: Clofazimine belongs to the WHO group 5 drugs recommended by the WHO to include in the treatment regiment for MDR-TB and XDR-TB patients [44]. The mechanism of action of this drug is not exactly defined [72]. The outer membrane of MTB may be the target of this drug [91]. A study showed that mutations in the reference strain H37Rv, regulator Rv0678 caused an overexpression of efflux pumps resulting in resistance to clofazimine[92].

Linezolid: This drug is also one of the WHO group 5 drugs recommended by the WHO for treatment of drug resistant TB [44][72]. It kills the cell by binding the the 50S ribosome subunit inhibiting protein synthesis [83]. Resistance to linezolid is considered to relate to

mutations in 23S rRNA[93], mutation T460C in rplC[94], and involvement of efflux pumps[95].

Bedaquiline: Bedaquiline is a newly developed anti TB drug. It has completed phase II clinical trials, but not phase III. This drug is recently included by the WHO belonging to group 5 drugs for MDR-TB treatment with interim policy guidance provided, to be used under conditional approval [44][96]. It has a novel mechanism of action by inhibiting the ATP synthase of MTB, which is encoded by *atpE* gene[97]. The most common mutation that causes resistance to bedaquiline is in the *atpE* gene[98]. However, only about 30% of resistant mutants had mutations in the *atpE* gene, other possible mechanisms of resistance is yet unknown[99].

Delamanid: This drug is also recently included in the group 5 drugs for treatment of MDR-TB by the WHO and is undergoing phase III clinical trials. The mechanism of action is to inhibit the mycolic acid synthesis [44][100]. Resistance mechanisms need to be elucidated [101].

1.5 Pathways of drug resistant TB

Two pathways are considered to cause the development of drug-resistant TB, including: acquired drug resistance and primary drug resistance. There are multiple factors involved in these pathways (Figure 1-5).

Figure 1-5. Pathways of drug resistant tuberculosis
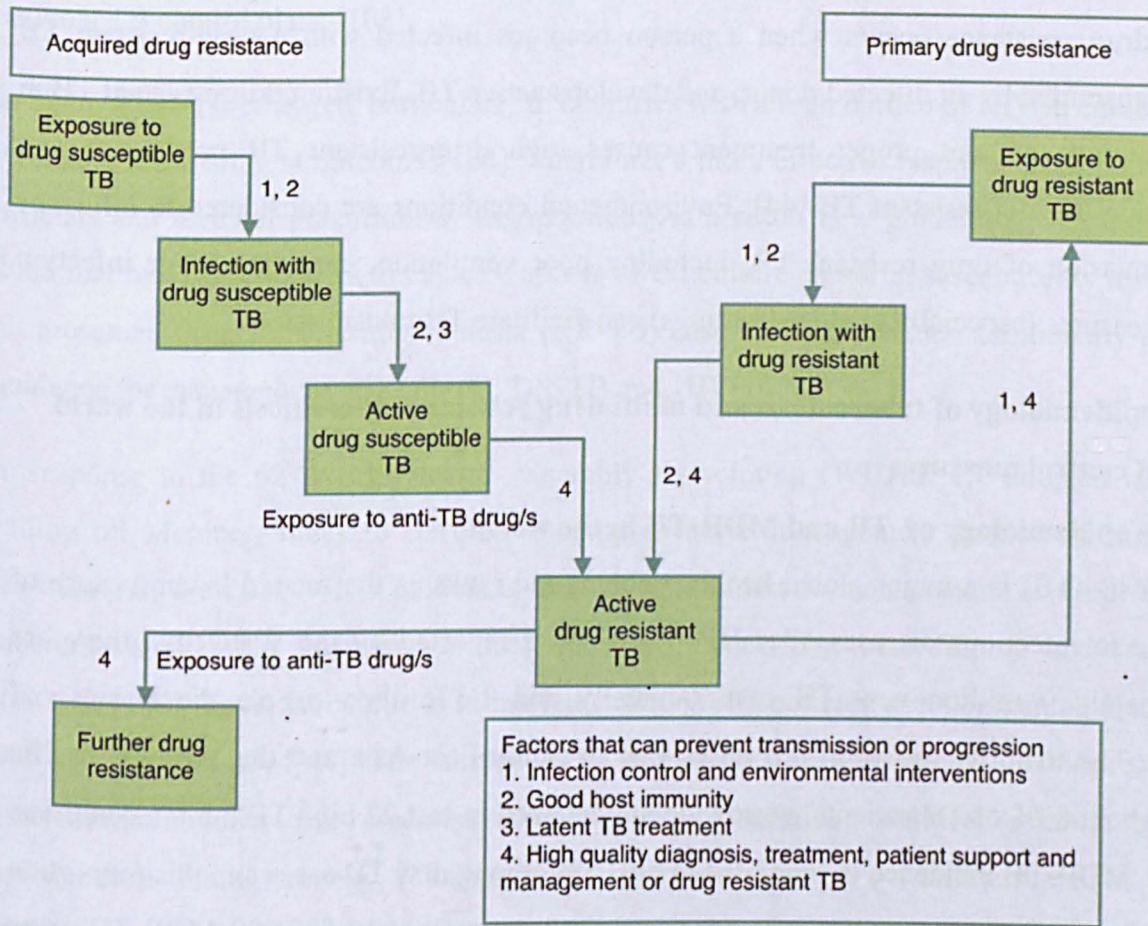
Acquired drug resistance is caused by poor treatment quality leading to the selection and stepwise amplification of mutant resistant strains (see above 'mechanism of drug resistance'). Factors that contribute to poor treatment outcomes include: (i) inappropriate treatment due to lack of treatment guidelines and training, poor patient education and treatment support, poor management of treatment response and adverse drug reaction, (ii) inadequate drug quality and supply due to stock out of drugs, unqualified drugs and poor storage conditions, (iii) poor patient's adherence to treatment. Cross cutting factors that contribute to both pathways leading to the spread of drug resistant TB include health system weakness and risk factors and social determinants. Week health services for diagnosis and treatment of TB involve insufficient financial resources, poor political commitment, mismanagement of supplies including

medicines and diagnostics commodities; and a poor functioning health information system. People who belong to vulnerable groups (HIV, drug abuse, alcoholism) or have poor socioeconomic condition have poor access to health care service and have higher risk of drug resistance development [44].

Primary drug resistance occurs when a person becomes infected with a drug-resistant TB isolate, transmitted by an infected donor, and develops active TB. Existing drug-resistant TB in the community without proper treatment causes high drug-resistant TB prevalence and transmission of drug-resistant TB [44]. Environmental conditions are considered to influence the transmission of drug resistant TB, including poor ventilation, crowding, poor infection control measures (especially in closed settings) can facilitate TB transmission.

1.6 The epidemiology of tuberculosis and multi drug resistant tuberculosis in the world and control measures

1.6.1 The epidemiology of TB and MDR-TB in the world

Tuberculosis (TB) is a major global health problem and ranks as the second leading cause of death due to infectious diseases after HIV/AIDS. It is reported by the WHO that there are approximately 9 million new TB cases annually and 1.5 million people die because of TB[102]. The majority (56%) of TB cases live in South-East Asia and the Western Pacific region. About 80% of TB patients worldwide are detected in just 22 high TB burden countries. Globally, MDR-TB incidence is estimated to be 3.5% among new TB cases and this proportion has been stable for recent years. It is estimated that approximately 500,000 MDR-TB cases emerge each year worldwide and between 5% and 7% of them develop XDR-TB [102].

1.6.2 Guidelines, framework and control measures for TB drug resistance recommended by the WHO

In 1997, the first report on drug resistance of tuberculosis (TB) in 35 countries revealed widespread drug resistance. The report recommended a more proactive approach to address multi-drug resistant tuberculosis (MDR-TB). As a result, the 'directly observed treatment-plus (DOT-plus) for MDR-TB" for directly observed treatment short course therapy (DOTS) approach for general TB control was established in 1999, followed by the Green Light Committee (GLC) in 2000. This GLC, hosted by the WHO, provides technical assistance and support to countries in accessing second line TB drugs. The first *Guidelines for establishing*

DOTS-Plus pilot projects for management of multidrug-resistant tuberculosis were published in 2000 and provided guidance for implementation for treatment of MDR-TB with second line anti-TB drugs. The 2006 WHO MDR-TB guidelines were to be in line with the 'Stop TB Strategy' (launched in 2005) which integrates management of MDR-TB into comprehensive national TB control plans [103].

In 2006, XDR-TB emerged, particularly in countries with a high burden of HIV in combination with poor TB treatment outcomes[104]. Therefore, a more effective response from both health officials and medical practitioners was required. As a result new guidelines were drafted in 2008 that required countries to enhance access to TB culture and drug susceptibility testing for all presumed drug resistant tuberculosis (DR-TB) cases. The guidelines additionally provide guidance for management of XDR-TB, DR-TB and HIV[105].

In response to the 62[nd]World Health Assembly's resolution (WHA62.15, adopted in 2009) calling on Member States to develop a comprehensive management framework for drug-resistant TB, the 2011 WHO guidelines for the programmatic management of drug resistant tuberculosis (PMDT) addresses critical questions concerning case finding and treatment strategies[106]. To assist countries in implementing WHO policies, the Companion Handbook was developed in 2014[44]. The current WHO framework for management of drug resistance tuberculosis includes five essential components: (1) sustained political commitment, (2) rational case finding strategy, (3) appropriate treatment strategy, (4) uninterrupted supply of quality assured anti-tuberculosis drugs, and (5) standardized recording and reporting systems.

Based on the pathways leading and factors contributing to drug resistant TB, five principle ways were recently recommended by the WHO (in 2014) to control drug resistant TB [44], including:

(i)   early diagnosis and quality treatment for drug-susceptible TB;

(ii)   early diagnosis and quality treatment for drug-resistant TB. Specific interventions for early diagnosis of drug resistant TB is to ensure appropriate diagnostic technologies to screen among risk groups including household contacts;

(iii) adequate infection control measures to minimize the risk of TB transmission in the populations, to be implemented at every level of heath care facility to household level;

(iv) well functioning health systems. It is recommended for the TB control programme to be integrated with other public health programmes for sharing of resources and joint activities;

(v) Targeting risk factors and social determinants as identified.

1.6.3 Policy for contact management

Tuberculosis contacts are defined as people who have close contact with infectious TB patients. They are recommended by the WHO to be actively and systematically investigated to detect TB infection and active TB and should be included in the national TB control programme (NTP) [18]. This systematic screening involves clinical assessment, testing and examinations or other procedures as needed. For children, tuberculin skin testing with purified protein derivative is also recommended. If active TB is not detected in the initial investigation, the close contact should be monitored[107]. This allows for early diagnosis and treatment to minimize the transmission in the community [18]. Depending on available resources, contact investigations can be performed for all index cases or only targeted to priority categories of index cases such as patients who have MDR-TB or XDR-TB, HIV co-infection, or who are young children [107]. TB in a child <5 years of age indicates that the infection likely was transmitted by his/her household members and warrants further investigation to find the source of infection, rather than find the secondary cases who were infected by the child[18].

Close contacts of MDR-TB and XDR-TB should be investigated using the same procedures as for contacts of drug-sensitive cases but more 'aggressively'. MDR-TB contact investigation should be integrated into the programmatic management of drug resistant TB (PMDT). Not only information about the contacts, information regarding the places that index patients resided or visited should be collected to investigate the risk of transmission in those sites [18]. In addition to the assessment and examination provided as for contacts of drug-susceptible TB, sputum investigation among contacts of MDR-TB need utilization of DST, ideally rapid diagnostic method such as Xpert MTB/RIF[44][18].In the settings that rapid DST is not available, close contacts of MDR-TB patients with clinical manifestation for TB should be

directly enrolled in empiric MDR-TB treatment to reduce mortality and transmission of drug resistance [44]. While the purpose investigation among contacts of drug-susceptible TB is for detection and treatment of both LTBI and active TB, investigation of MDR-TB contacts will focus on diagnosis and treatment of active TB [44].

1.7 Introduction to Viet Nam and its healthcare system

1.7.1 General information on health and health system

Viet Nam is located in South East Asia region with a population of 91 million in 2014. Viet Nam is divided into 63 provinces and cities. The provinces and cities are divided into districts, which are subdivided into communes. There are 54 different ethnic groups housed in Viet Nam; among these, the Kinh people are predominant (accounting for 86.2% of the whole population). Any health program is more difficult by increasing distances from the big cities to the remote areas. Health services are weaker in the rural areas where 70% of the population lives[108][109].

The health status of people in Viet Nam has improved significantly over the last few decades. Level of basic health indicators are higher compared with that in other countries with equal income per capita; such as, life expectancy at birth, maternal mortality ratio, infant and child mortality rate, child malnutrition rate, and malaria morbidity and mortality[109]. The average life expectancy of the Vietnamese people increased considerably from 72.9 in 2010 to 73.1 in 2013 (Table 1-3)[109-112]. During 2001-2008, the infant mortality rate fell sharply from 30‰ to 15‰ [104]. This rate gradually declined from 2010-2013 [109-112]. The mortality rate of under-five fall from 58‰ in 2001, to 27.5‰ in 2005 and 25.0‰ in 2009 [104], it continued to decreased from 23.8‰ to 23.1‰ during 2010 and 2013[109-112]. However the TB prevalence and HIV prevalence has not decreased.

Currently, TB ranks third in the list of important communicable diseases in Viet Nam[109]. Although the annual number of reported new HIV was considered to decline gradually, the cumulative indicators did not decrease due to unpredictable trends in risk factors for HIV such as injecting drug use and commercial sex work[114]. HIV prevalence in adults is approximately 0.24 %, which is similar with that for Malaysia and Indonesia, but lower than for Thailand and Cambodia[115]. Disparities in health status between regions and between population groups are a concern. The regions with low level of basic health indicators are those

with geographical difficulties to access to health services, unsafe water and high poverty proportion[109].

Table 1-3.Basic health indicators achieved by the national health program from 2010-2013 (source: Health Partnership Group, Joint annual health review 2011-2014)

Indicators	2010	2011	2012	2013
Population size (million)	86.9	87.8	88.8	89.7
Average life expectancy (years)	72.9	73.0	73.0	73.1
Infant mortality rate (‰)	15.8	15.5	15.4	15.3
Under -five mortality rate	23.8	23.3	23.2	23.1
HIV/AIDS prevalence rate (%)	0.21	0.22	0.237	0.242

1.7.2 Epidemiology of TB and drug resistant TB

Viet Namis ranked 12th among 22 high burden countries with TB, and 14th among 27 countries with a high burden of MDR-TB. Viet Nam was one of the first high-burden countries to achieve the WHO target of detecting 70% of all new sputum smear-positive cases arising each year, and of treating 85% of the detected cases successfully since 1997[116][117]. While TB incidence in Viet Nam was predicted by mathematical models to decline about 11% (range 8-12)[118] if the target was achieved, the notification rate of new smear-positive TB showed no decline from 1997-2006[119].The question for the Viet Nam NTP regarding the accuracy of the WHO estimation was answered by the result from a national TB prevalence survey conducted in 2006-2007. It was shown that the prevalence of TB was 1.6 times as high as previously estimated, revealing that many cases remain undiagnosed[27].

The Fourth National Anti-Tuberculosis Drug Resistance Survey (DRS) in Viet Nam showed an increasing trend of MDR-TB among new and previously cases compared with the three previous drug resistance surveys conducted in Viet Nam in 1996, 2003 and 2005. The MDR-

TB rate increased from 2.3% in 1996–1997 to 2.7% in 2005 and 4.0% in 2011 among new cases[120].

In 2013, the incidence of TB in Viet Nam is estimated at 144 per 100,000 population per year and the estimated prevalence is 209 cases per 100,000 population. The mortality rate of TB (exclude HIV+TB) is reported at 19 per 100,000 population[102]. The proportion of TB cases with resistance to any drug was 32.7% and 54.2% among new and previously treated cases, respectively. Resistance levels of streptomycin (30.0%) and isoniazid (22.4) were higher than rifampin (6.7 %) and ethambutol (4.5 %) resistance levels. The proportion of TB cases with MDR-TB among new and retreatment cases is estimated to be 4% (95%CI 2.5-5.4) and 23% (95%CI 16.7-29.9), respectively, with approximately 6% among TB cases co-infected with HIV [102][120]. These proportions are equal to the levels in the countries with high burden of MDR-TB (4.2%, 95%CI 2.1–6.2 and 21%, 95%CI 12–30, respectively), but slightly higher than the global proportions (3.6%, 95%CI 2.1–5.1and 20.2%, 95%CI 13.3–27.2, respectively)[17]. According to the TB drug resistance survey conducted in Viet Nam from 2011-2012 showed that the estimated proportion of XDR-TB among MDR-TB is 5.6% (unpublished data). There are estimated to be about 5,100 MDR-TB and 290XDR-TB cases among notified TB cases per year.

1.7.3 The framework and policy of Viet Nam for drug resistance management

Viet Nam started to develop the plan for controlling MDR-TB in 2007 and this plan was approved by the GLC to be implemented in the period 2007-2011[121]. In 2008, the first guidelines for programmatic management of DR-TB in Viet Nam was developed, which adopted the WHO recommended five-component frame work [122]. Case finding and treatment strategies programmatic management of drug resistant of Viet Nam was updated in line with the WHO recommendation in a step-wise manner. Viet Nam specific conditions regarding capacity for diagnosis and treatment of drug resistant TB, financial and human resources, were taken into consideration. Regarding case finding strategies used in Viet Nam, we refer to chapter 2 of this Thesis (MDR-TB control policies and practices in Viet Nam for case finding strategy).

Treatment strategy

In accordance with the WHO guidelines, Viet Nam adopted the standardized treatment regimen based on results of the 3rd national drug resistance survey data for MDR-TB patients. Based on the WHO recommended principles, the treatment design selected drugs including Ethambutol, Pyrazinamide, Kanamycin (or Capreomycin if Kanamycin is intolerable), Levofloxacin, Pro-Ethionamide, Cycloserines (PAS if Cycloserine is intolerable). As regards of treatment duration, to be in line with the most updated WHO recommendation in 2014[44], the current treatment guideline adopts 8 and 20 months for intensive phase and total duration of treatment for newly diagnosed MDR-TB patients, respectively. This recommendation was based on a meta-analysis which included more than 9000 treatment episodes for MDR-TB patients [106]. The analysis found that the adjusted relative risk for cure peaked at a treatment duration between 7.1 and 8.5 months, and between 18.6 and 21.5 months for intensive phase and whole treatment course, respectively. However, only observational studies without randomized controlled trials were included in this meta-analysis, so the quality of evidence can be considered as low [106].

1.7.4 The structure and organisation of the national TB control programme of Viet Nam

The network and organization of Viet Nam NTP and function of TB units by levels

Regarding the organization of the health care sector in Viet Nam, there are four administrative levels that form of a four-tiered pyramid. On top is the Ministry of Health (MOH), the highest-level authority in the health sector. The second tier is the provincial Department of Health (DOH) that provides health services for the population at the provincial level. The next level is the District Health Centers (DHC), responsible for health care activities in the districts and their communes. The fourth tier consists of the Commune Health Centers (CHC) that serve people in the communities. Administrative directions are operated in the top-down order from the MOH, province, district to communal levels. In Viet Nam, private health care facilities are common, especially in larger cities. In the 23 provinces that have private-public health services mixed in TB control (PPM), there are 26,648 private health care facilities available[123].

Similar to the general health care sector, the TB program is also organized by four levels in Viet Nam. The top level is the central (national TB control programme), followed by provincial TB programme, district TB units and communal health post. The TB programme at

the central level is located in three sites including (i) the National Lung Hospital (NLH) in Hanoi, (ii) the National Lung Hospital of 74 (NT.74) in Vinh Phuc province and (iii) the National Lung Hospital of 71 (NT.71) in Thanh Hoa province. The central TB programme is administratively under direction of the MOH, and technically provides direction to provincial TB programmes. Likewise, the provincial TB programmes are administratively under management of the DOH, and provide technical management to the district levels. From district to communal levels, the TB program is fully integrated in the primary care system. The district level provides both administrative and technical direction to the communal level (Figure 1-6).

The PMDT is fully integrated into the NTP. The infrastructure of the TB control network is also used for PMDT implementation (Figure 1-6) [114]. As a result, the PMDT has four different levels: central, provincial, district and communal level.

Figure 1-6.Organizational structure of the TB programme in Viet Nam.
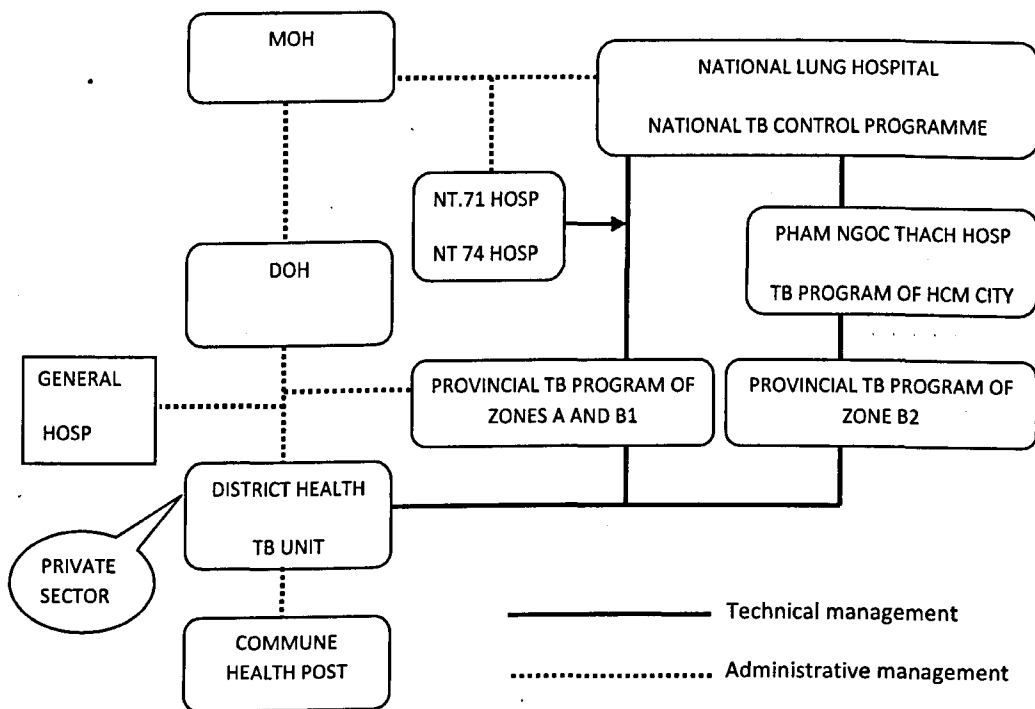
At the central level, the PMDT task force has been formed as one of the technical groups under the official directive of the NTP Director. The main function of the central PMDT task force is to develop action plans, mobilize funding, ensure sufficient diagnostics and treatment supplies,

supervise and monitor the implementation and progress of PMDT, provide training and technical assistance to peripheral levels. At provincial levels, the main function is to provide diagnosis, treatment, case management and follow up. However, the actual PMDT varies between provinces due to differences in staffing, diagnostic and treatment capacities. A province can have a treatment center, a treatment site, a diagnosis center, a diagnosis site or a cultural laboratory based on the following definitions:

- The treatment center is defined as a facility having bed capacity to hospitalize local MDR-TB patients and patients from surrounding provinces.
- Treatment site is a facility having bed capacity to hospitalize MDR-TB patients resided in the province only.
- Adjacent province is referred to a province having no bed capacity to hospitalize MDR-TB patients. Its responsibility is to provide ambulatory treatment after patients discharged from treatment centers in other provinces
- Diagnosis center is a laboratory with capacity to perform DST for first and second line anti-TB drugs.
- Diagnosis site is a laboratory with capacity to perform Xpert MTB/RIF to detect rifampicin resistance.
- Culture laboratory is a facility approved by the NTP to perform culture to follow-up the treatment of MDR-TB patients.

In case a province has no hospitalization capacity for MDR-TB patients, patients are referred to an adjacent province with this capacity.

The number of provinces with a PMDT center increased from 1 to 45 provinces between 2009 and 2015. The network expansion for PMDT regarding treatment and diagnosis system is presented in Table 1-4.

Table 1-4. Network expansion of the Viet Nam PMDT between 2009 and 2015.

	2009	2010	2011	2012	2013	2014	2015
Total PMDT provinces	1	6	20	35	35	41	45
Treatment center	1	6	6	10	10	10	10
Treatment sites					17	19	24
Adjacent provinces			14	25	8	12	11
Diagnosis center	2	2	2	2	2	2	2
Diagnostic sites for PMDT				14	25	40 (*)	60 (**)
Culture laboratory for PMDT	1	6	17	19	19	19	19

(*) located in 31 PMDT provinces; (**) plan to procure additional 20 Xpert machines to have 60 machines by the end of 2015 to cover 45 PMDT provinces

At the district level, the PMDT is managed by the district TB unit (DTU), which is the basic unit in the PMDT network. The main function of DTU is to identify presumed MDR-TB and transfer sputum samples for diagnosis, provide treatment with direct observation for patient when they discharge the provincial hospital, supervise treatment supporters at communal level. At the commune level, the PMDT is managed by commune health staff. They are involved to support patients during ambulatory treatment, clinically assess to identify presumed TB and MDR-TB including symptomatic contact and refer them for screening[122].

As far as the involvement of the private sector is concerned, at the moment, the collaboration between the NTP and private sectors is being implemented for detection and treatment of general TB patients, and not for MDR-TB patients specifically. The PMDT have requested the private sector to comply with national guidelines in treatment of MDR-TB and to report to the NTP for cases enrolled and treatment outcome. Thus far the private sector does not comply

fully in reporting MDR TB cases. However, of those reported, the treatment outcome data show a very high default rate of up to 75% in 2011 in Ho Chi Minh city[124].

The TB laboratory network and system in Viet Nam

It is recommended by the WHO that the essential laboratory services for PMDT should involve both mycobacteriology and clinical laboratories. Mycobacteriology laboratories are required to be able to identify *M. tuberculosis* and perform DST to at least rifampicin and isoniazid. They also should have culture capacity for monitoring patient's response to treatment. The target is to have at least one culture laboratory per 5 million population [44][125]. The laboratory infrastructure in Viet Nam for PMDT is organized in the WHO recommended pyramid structure (Figure 1-7). Level I is for peripheral laboratories located in district level. The main function of these laboratories is doing smear microscopy while Xpert machines are only provided in some districts in Ho Chi Minh City and Hanoi. So far there are 979 microscopy units available including 730 units located in districts, 249 units located in general hospitals and in prison health units (equal to district level). There are only 6 Xpert machines available in the district level. Level II is for intermediate laboratories located in the provincial level. In addition to capacity to perform smear in all laboratories, level II laboratories compose of diagnosis sites (equipped with Xpert machines) and culture laboratories responsible for doing culture (solid and liquid) to monitor patient's response to treatment (culture conversion).

The laboratory network, especially in level II was expanded over time to meet the increasing requirements for PMDT. The population of Viet Nam in 2014 was reported at about 90 million, and there are 19 culture laboratories for PMDT so far to meet the WHO requirement (refer to the table 1-7 for number of diagnosis sites and culture laboratories). Level III laboratories (diagnosis centers) have DST capacity in addition to functions of levels I and II. There were two level III laboratories, one is the national reference laboratory located in National Lung Hospital (Hanoi) and one is the regional laboratory located in Pham Ngoc Thach hospital in Ho Chi Minh City. These two laboratories can do molecular testing, conventional DST to first line and second line TB drugs.

Figure 1-7. Laboratory organizational structure of the NTP in Viet Nam.

Supranational laboratory, IMVS

Level III/central, regional

02 Diagnosis centers: 1 National Reference laboratory in National Lung hospital, Hanoi; 1 regional laboratory in Pham Ngoc Thach hospital, Ho Chi Minh City
EQA of smears; monitoring and supervision of culture laboratories

DST
Culture
Xpert
Smear

Level II/ intermediate

Located in provincial level
• Diagnosis sites with Xpert machines
• Culture laboratories

Xpert
Culture
Smear

Level I/periferal

In district (or equal district) level
979 microscopy units, 6Xperts

Microscopy
Xpert

The policy of Viet Nam is to ensure quality of diagnosis and treatment monitoring of drug resistant tuberculosis in all TB laboratories. The infrastructure should be sufficient for performing sputum microscopy, culture and DST with proper bio-safety. However, the policy for clinical laboratory development is not mentioned in any guidelines for TB or PMDT. Services for this basic examination were set up by provincial health departments or TB hospitals themselves, and not by the NTP. In PMDT implementing sites, clinical laboratory services are considered to fulfill the minimum required testing for treatment evaluation.

Two level III laboratories have the link with the supranational laboratory in Adelaide, Australia, the Institute of Medical & Veterinary Science (IMVS), for DST proficiency testing. These level III laboratories also have responsibility for smear microscopy external quality assurance (EQA), monitoring and supervision of culture laboratories. In 2012 the guidelines to ensure the quality control of a culture laboratory were developed with a check list for culture

laboratory supervision[125]. However, quality assurance system for culture in accordance with these guidelines has not been practiced adequately, and the completed checklist after supervision visits were not analyzed for strength, weaknesses of culture laboratory system in the country yet. So far there is no established EQA programs specific for Xpert MTB/RIF. To ensure the best performance of Xpert MTB RIF, Viet Nam has a yearly plan for calibration of Xpert machines and a contracted maintenance services.

1.7.5 Resources for PMDT in Viet Nam

The mid-term development plan for the period 2007-2011[126] and 2011-2015[127] included PMDT activities and were submitted and approved by the Global Fund to Fight AIDS, TB and Malaria (GFATM). About 40% of this funding source was allocated for PMDT annually to conduct its activities from 2009- 2015 (Table 1-5). Approximately 90% of the PMDT is supported by the GFATM. Other sources have also supported the PMDT including (i) government for first line drugs (FLDs) as part of composition for MDR-TB treatment regimen, (ii) budget from the *President's Emergency Plan for AIDS Relief (*PEPFAR) under the TBCARE project for human resource development, technical assistance and some facility upgrading activities.

The average cost for one MDR-TB case detected and treated in Viet Nam is approximately USD 3,500including USD 2,000 for SLD, as opposed to about100 USD required for first line drugs to treat a susceptible case[128]. About ninety percent of PMDT budget is for SLD, the other cost is for detection, training and case management. Budget allocated to case finding activities includes procurement of consumables (material for sputum packaging, test kits and reagents), cost for sputum refferal, and reimbursement for testing. For the period 2016-2017, the PMDT increased the capacity to provide diagnosis and treatment for an additional 5,400 MDR-TB patients. To prepare for funding sustainability in the future, the NTP has sent an official request to provincial authorities and local TB control programmes, to develop their own strategic plan to mobilize more local financial support for TB control including PMDT for the period from 2016-2020.

Table 1-5. GFATM funding for the NTP and PMDT from 2009-2015

Year	2009	2010	2011	2012	2013	2014	2015
PMDT Budget (USD)	151,110	1,478,723	3,703,731	4,011,090	4,684,019	6,867,387	8,286,033
Total amount for NTP (USD)	3,332,387	4,018,737	10,344,005	10,749,894	13,103,832	12,992,319	16,863,747
% PMDT budget	4.53%	36.80%	35.81%	37.31%	35.75%	52.86%	49.14%

The total number of personnel engaged in TB control in the Viet Nam is: 19,174 healthcare workers (2.21/10,000 inhabitants). The number of staff working for TB at provincial, district and communal level are 5,116 (0.59 / 10,000 inhabitants), 3,475 (0.4 / 10,000 inhabitants) and 11,840 (1.37/10,000 inhabitants), respectively[129].

1.7.6 Indicators to monitor and evaluate the PMDT

Indicators developed by GFATM in collaboration with Stop TB Department and the Stop TB Partnership for monitoring MDR-TB management were adopted by Viet Nam's PMDT and used in this thesis. This set of indicators cover the main activities of PMDT including diagnosis, enrollment, treatment outcome and supply management for MDR-TB[130]. The list of these indicators is presented in Chapter 2.

1.8 Outline of the thesis

Viet Nam is a country with a high TB burden and management of MDR-TB in Viet Nam is one of the main objectives of the TB control programme. Viet Nam started treatment for MDR-TB since 2009 and scaled up the network to manage MDR-TB to 45 provinces by 2015. The number of MDR-TB detected and enrolled on treatment increased over the past six years from 100 patients to 1500 patients per year. Viet Nam increased the utilization of rapid diagnostic testing since 2012 to detect MDR-TB. In parallel, Viet Nam improved the supply chain

management system to access SLD to treat detected MDR-TB patients[124][128].Viet Nam should use these increased capacities to optimize the early detection of patients, and proper treatment to decrease the source of infection and diminish the amplification of drug resistance. This thesis, therefore, assesses current case finding strategies for TB and MDR-TB in Viet Nam to find targets to improve case finding to enable the NTP to detect more MDR-TB cases sooner.

The first objective of this research is to assess MDR-TB control policies and practices in Viet Nam, with a special focus on case-finding strategy to see what the challenges are and how it can be improved. The second objective is to assess screening practices among a high risk group for MDR-TB including household contacts and other MDR-TB presumptives.Currently, the contacts are recommended by the NTP to go for screening whenever they have TB presumed symptoms. This passive case finding may not identify the MDR-TB cases who do not go for screening, or diagnose MDR-TB at a too late stage when the patients are seriously ill. The third objective of this thesis is to evaluate whether social-network analysis, an active approach for screening among contacts of MDR -TB cases in Viet Nam can improve MDR-TB case detection. The outline of the different chapters is as follows:

- Chapter 2 presents the main outcomes of the assessment for MDR-TB control policies and practices in Viet Nam for case finding strategy.

- Chapter 3 describes screening practice of household contacts of smear positive tuberculosis patients in Viet Nam.

- Chapter 4 describes screening practices among MDR-TB presumptive cases in areas of Viet Nam with PMDT.

- Chapter 5 presents the results of the contact tracing by Social Network Analysis (SNA) to enhance Multi-Drug Resistant Tuberculosis Case Finding in Hanoi in Viet Nam.

- Chapter 6 provides a general discussion of the findings described in this thesis and suggestions to improve case finding strategy of MDR-TB as well as for further research.

Reference

1. Cole ST, Brosch R, Parkhill J, Garnier T, Churcher C, Harris D, et al. Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence. Nature. 1998;393:537-44.

2. S. M. Blevins, M. S. Bronze. Robert Koch and the 'golden age' of bacteriology. Int. J. Infect. Dis., 2010; 14: 744–51.

3. de Jong BC, Antonio M, Gagneux S. Mycobacterium africanum - review of an important cause of human tuberculosis in West Africa. PLoS Negl Trop Dis. 2010; 4(9): e744:doi:10.1371/journal.pntd.0000744.

4. Enarson DA, Rieder HL, Arnadottir T, Trébucq A. Management of tuberculosis. A guide for low income countries. (Fifth Edition). In: Disease IUATaL, editor. 5 ed. Paris: International Union Against Tuberculosis and Lung Disease; 2000. p. 1-89.

5. Caminero Luna JA. A tuberculosis guide for specialist physicians. International Union Against Tuberculosis and Lung Disease. 68 boulevard Saint Michel, 75006 Paris – France; 2004. p. 1-411.

6. Rieder HL. Epidemiologic basis of tuberculosis control. In: International Union Against Tuberculosis and Lung Disease, editor. 1 ed. Paris: International Union Against Tuberculosis and Lung Disease; 1999. p. 1-162.

7. Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis infection. N Engl J Med. 2015;372(22):2127-35.

8. World Health Organization. Guidelines on the management of latent tuberculosis infection. World Health Organization Document. 2015;WHO/HTM/TB/2015.01:1-33.

9. Marks GB, Bai J, Simpson SE, Sullivan EA, Stewart GJ. Incidence of tuberculosis among a cohort of tuberculin-positive refugees in Australia: reappraising the estimates of risk. Am J Respir Crit Care Med. 2000;162(5):1851-4.

10. Rieder HL, Cauthen GM, Bloch AB, Cole CH, Holtzman D, Snider DE, Jr., et al. Tuberculosis and acquired immunodeficiency syndrome - Florida. Arch Intern Med. 1989;149:1268-73.

11. Egwaga SM, Cobelens FG, Muwinge H, Verhage C, Kalisvaart N, Borgdorff MW. The impact of the HIV epidemic on tuberculosis transmission in Tanzania. AIDS. 2006;20:915-21

12. Walia K. Symposium on HIV & TB. 4. Current issues in HIV / TB co-infection. Indian J Tuberc. 2002;49:21-6.

13. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. World Health Organization Document. 2006;WHO/HTM/TBM/2006.371:1-41.

14. Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. Int J Tuberc Lung Dis. 2004;8:286-98.

15. Alisjahbana B, van Crevel R, Sahiratmadja E, den Heijer M, Maya A, Istriana E, et al. Diabetes mellitus is strongly associated with tuberculosis in Indonesia. Int J Tuberc Lung Dis. 2006;10:696-700.

16. Lonroth K, Williams B, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis – a systematic review. BMC Public Health. 2008;8:289.

17. World Health Organization. Global tuberculosis report 2013. Geneva, Switzerland: World Health Organization Document. 2013;WHO/HTM/TB/2013.11:1-289.

18. World Health Organization. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva, Switzerland: World Health Organization Document. 2012.WHO/HTM/TB/2012.9

19. World Health Organization. Tuberculosis Care with TB-HIV Co-management. Geneva, Switzerland: World Health Organization Document. 2007. WHO/HTM/HIV/2007.; WHO/HTM/TB/2007.

20. Childhood TB: Training Toolkit, WHO, Geneva, 2014 www.who.int/tb/challenges/childtbtraining_manual/en/ - See more at: http://www.tbfacts.org/symptoms-tb/#sthash.xcudY3gc.dpuf

21. M. P. Golden, H. R. Vikram.Extrapulmonary tuberculosis: An overview. Am. Fam. Physician. 2005. 72 (9): 1761–68.

22. Rook GAW, Dheda K, Zumla A. Immune responses to tuberculosis in developing countries: implications for new vaccines. Nature Rev. 2005;5:661-7.

23. World Health Organization. Treatment of tuberculosis: guidelines for national programmes. Fourth edition. World Health Organization Document. 2010;WHO/HTM/TB/2009.420:1-147.

24. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision. Geneva, Switzerland: World Health Organization Document. 2013; WHO/HTM/TB/2013.2

25. World Health Organization. Early detection of tuberculosis. An overview of approaches, guidelines and tools. World Health Organization Document. 2011;WHO/HTM/STB/PSI/2011.21:1-24.

26. English.R. G, Bachmann.M. O., Bateman.E. D, Zwarenstein.M. F, Fairall.L. R, Bheekie.A, Majara.B. P, Lombard.C, Scherpbier., Ottomani.S. E. Diagnostic accuracy of an integrated respiratory guideline in identifying patients with respiratory symptoms requiring screening for pulmonary tuberculosis: a cross-sectional study. BMC Pulm. Med., 2006. 6: 1-26.

27. Hoa NB, Sy DN, Nhung NV, Tiermersma EW, Borgdorff MW, Cobelens FGJ. National survey of tuberculosis prevalence in Viet Nam. Bull World Health Organ. 2010;88:273-80.

28. Kumar D, Watson JM, Charlett A, Nicholas S, Darbyshire JH. Tuberculosis in England and Wales in 1993: results of a national survey. Thorax. 1997;52:1060-7.

29. Humphries MJ, Gabriel M, Lee YK. Spinal tuberculosis presenting with abdominal symptoms - a report of two cases. Tubercle. 1986;67:303-7.

30. Walker GF. Failure of early recognition of skeletal tuberculosis. BMJ. 1968;1:682-3.

31. Klimach OE, Ormerod LP. Gastrointestinal tuberculosis: a retrospective review of 109 cases in a district general hospital. Quarterly J Med. 1985;56:569-78.

32. Lambrianides AL, Ackroyd N, Shorey BA. Abdominal tuberculosis. Br J Surg. 1980;67:887-9.

33. Steven A.Sahn, Thomas A.Neff. Military Tuberculosis. Denver, Colorado, The American Journal of Medicine 1974; 56:495-505

34. Korzeniewska-Kosela M, Krysl J, Müller N, Black W, Allen EA, FitzGerald JM. Tuberculosis in young adults and the elderly. A prospective comparison study. Chest. 1994;106:28-32.

35. World Health Organization. Implementing tuberculosis Policy framework, Policy framework. Geneva, Switzerland: World Health Organization Document. 2015; WHO/HTM/TB/ 2015.11

36. Barker. R. D.Clinical tuberculosis.Med. (United Kingdom). 2012. 40: 340–45.

37. Reznik M, Ozuah PO. Tuberculin skin testing in children. Emerg Infect Dis. 2006;12 (5) :725-8.

38. International Union Againsn Tuberculosis and Lung Diseases, Technical Guide, Sputum Examination for Tuberculosis by Direct Microscopy in Low Income Countries, Fifth edition . 68 boulevard Saint Michel, 75006 Paris, France. 2000, pp. 2–15.

39. World Health Organization .Fluorescent light-emitting diode (LED) microscopy for diagnosis of tuberculosis, Policy statement. Geneva, Switzerland: World Health Organization 2011. WHO/HTM/TB/ 2011.8

40. Steingart KR, Ramsay A, Pai M. Optimizing sputum smear microscopy for the diagnosis of pulmonary tuberculosis. (Editorial). Expert Rev Anti-Infect Ther. 2007;5:327-31.

41. den Hertog AL, Daher S, Straetemans M, Scholing M, Anthony RM. No added value of performing Ziehl-Neelsen on auramine-positive samples for tuberculosis diagnostics. Int J Tuberc Lung Dis. 2013 Aug;17(8):1094-9

42. F. Rageade, N. Picot, A. Blanc-Michaud, S. Chatellier, C. Mirande, E. Fortin, A. van Belkum. Performance of solid and liquid culture media for the detection of Mycobacterium tuberculosis in clinical materials: meta-analysis of recent studies. Eur. J. Clin. Microbiol. Infect. Dis. 2014. 33:867–70.

43. World Health Organization . Use of liquid TB culture and drug susceptibility testing (DST) in low and medium income settings. Policy statement. Geneva, Switzerland: World Health Organization 2007.

44. World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland:World Health Organization Document. 2014;WHO/HTM/TB/2014.11:1-403.

45. World Health Organization. Molecular line probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis (MDR-TB). Policy statement. Geneva, Switzerland: World Health Organization 2008.

46. World Health Organization. Xpert MTB/RIF implementation manual, Technical and Operational 'How-to', Practical considerations, Geneva, Switzerland: WHO 2014. WHO/HTM/TB/2014.1

47. M. J. van der Werf, M. W. Langendam, A Sandgren, D. Manissero. Lack of evidence to support policy development for management of contacts of multidrug-resistant tuberculosis patients: two systematic reviews. Int J Tuberc Lung Dis. 2012;16 (3):288-96.

48. D. Heemskerk, M. Caws, B. Marais, J.Farrar.Tuberculosis in Adults and ChildrenSpringer Briefs in Public Health. 2015: 1-66. DOI 10.1007/978-3-319-19132-4

49. Espinal MA et al. Determinants of drug-resistant tuberculosis: analysis of 11 countries. International Journal of Tuberculosis and Lung Disease, 2001, 5:887–893.

50. National Collaborating Centre for Chronic Conditions.Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London, Royal College of Physicians, NICE (National Institute for Health and Clini- cal Excellence), 2006.

51. American Thoracic Society, CDC, Infectious Diseases Society of America. Treatment of tuberculosis. Morbidity and Mortality Weekly Report: Recommendations and Reports, 2003, 52(RR-11):1–77

52. World Health Organization. Essential prevention and care interventions for adults and adolescents living with HIV in resource-limited settings. Geneva, Switzerland. World Health Organization, 2008

53. Thwaites GE et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. New England Journal of Medicine, 2004, 351:1741–1751

54. Ramaswami S, Musser JM. Molecular genetic basis of antimicrobial agent resistance in Mycobacterium tuberculosis: 1998 update. Tuber Lung Dis. 1998;79:3-29.

55. da SilvaP. E. A. , PalominoJ. C., Molecular basis and mechanisms of drug resistance in Mycobacterium tuberculosis: Classical and new drugs,J. Antimicrob. Chemother.,2011. 66: 1417–30.

56. RossiE. D., AínsaJ. a., RiccardiG. Role of mycobacterial efflux transporters in drug resistance: An unresolved question. FEMS Microbiol. Rev.2006. 30: 36–52

57. S. Shaikh, J. Fatima, S. Shakil, S. M. D. Rizvi, and M. A. Kamal. Antibiotic resistance and extended spectrum beta-lactamases: Types, epidemiology and treatment. Saudi J. Biol. Sci., 2015. 22(1): 90–101

58. J. Tham. Extended-spectrum beta-lactamase producing-enterobacteriaceae: Epidemiology, Risk Factors, and Duration of Carriage., Lund University. 2010. 17(4):140–44.

59. Kochi A, Vareldzis B, Styblo K. Multidrug-resistant tuberculosis and its control. Res Microbiol. 1993;144:104-10

60. R. Johnson, E. M. Streicher, E. Louw, R. M. Warren, P. D. Van Helden, T. C. Victor. Drug Resistance in Mycobacterium tuberculosis. Horiz. Sci. Press.2003;. 8: 97–112.

61. H. L. David. Probability distribution of drug-resistant mutants in unselected populations of Mycobacterium tuberculosis. Appl. Microbiol. 1970; 20(5): 810–14

62. de Steenwinkel JEM, ten Kate MT, de Knegt GJ, Kremer K, Aarnoutse RE, Boeree MJ, et al. Drug susceptibility of Mycobacterium tuberculosis Beijing genotype and association with MDR TB. Emerg Infect Dis. 2012;18:660-3

63. FordC. B, ShahR. R, MaedaM. K., GagneuxS, MurrayB, CohenT, JohnstonJ. C, GardyJ, LipsitchM. Mycobacterium tuberculosis mutation rate estimates from different lineages predict substantial differences in the emergence of drug resistant tuberculosis. Nat Genet. 2014; 45(7):784–90.

64. Zhang Y, Yew WW. Mechanisms of drug resistance in Mycobacterium tuberculosis. [State of the Art Series. Drug-resistant tuberculosis. Number 1 in the series]. Int J Tuberc Lung Dis. 2009;13:1320-30.

65. TraunerA., BorrellS., ReitherK., GagneuxS. Evolution of drug resistance in tuberculosis: Recent progress and implications for diagnosis and therapy. Drugs. 2014; 74: 1063–72

66. Bonnet M, Pardini M, Meacci F, Orrù G, Yesilkaya H, Jarosz T, et al. Treatment of tuberculosis in a region with high drug resistance: outcomes, drug resistance amplification and re-infection. PLoS ONE. 2011;6(8): e23081:doi:10.1371/journal.pone.0023081.

67. RattanA, KaliaA, AhmadN. Multidrug-Resistant Mycobacterium tuberculosis : Molecular Perspectives. Emerg. Infect. Dis. 1998; 4(2): 195–209

68. BhaktaS., BesraG. S., UptonA. M., ParishT., Sholto-Douglas-VernonC., GibsonK. J. C., KnuttonS., GordonS., DaSilvaR. P., AndertonM. C., SimE., Arylamine N-acetyltransferase is required for synthesis of mycolic acids and complex lipids in Mycobacterium bovis BCG and represents a novel drug target. J. Exp. Med., 2004; 199(9): 1191–99.

69. Gagneux S, Burgos MV, DeRiemer K, Enciso A, Muñoz S, Hopewell PC, et al. Impact of bacterial genetics on the transmission of isoniazid-resistant Mycobacterium tuberculosis. PLoS Pathogens. 2006;2(6): e61.

70. Hazbón, M.H.; Brimacombe, M.; Bobadilla del Valle, M.; Cavatore, M.; Guerrero, M.I.; Varma-Basil, M.; Billman-Jacobe, H.; Lavender, C.; Fyfe, J.; García-García, L.; et al. Population genetics study of isoniazid resistance mutations and evolution of multidrug-resistant Mycobacterium tuberculosis. Antimicrob. Agents Chemother. 2006, 50, 2640–2649

71. Fenner, L.; Egger, M.; Bodmer, T.; Altpeter, E.; Zwahlen, M.; Jaton, K.; Pfyffer, G.E.; Borrell, S.; Dubuis, O.; Bruderer, T.; et al. Effect of mutation and genetic background on drug resistance in Mycobacterium tuberculosis. Antimicrob. Agents Chemother. 2012, 56 (6): 3047–53

72. Palomino.J, Martin.A. Drug Resistance Mechanisms in Mycobacterium tuberculosis. Antibiotics. 2014; 3: 317–40

73. Shi W, Zhang X, Jiang X, Yuan H, Lee JS, Barry CE 3rd, Wang H, Zhang W, Zhang Y. Pyrazinamide inhibits trans-translation in Mycobacterium tuberculosis. Science. 2011 Sep 16;333(6049):1630-2

74. Zhang Y, Mitchison D. The curious characteristics of pyrazinamide: a review. Int J Tuberc Lung Dis. 2003;7:6-21.

75. Chang KC, Yew WW, Zhang Y. Pyrazinamide susceptibility testing in Mycobacterium tuberculosis: a systematic review with meta-analyses. Antimicrob Agents Chemother. 2011;55:4499-505.

76. Zimhony J. W. J, Cox O, Welch JS, VilchèzeJT, Pyrazinamide inhibits the eukaryotic. Nat Med. 2000; 6(9): 1043–7

77. DenkinS., Volokhov. D. Chizhikov.V, Zhang.Y, Microarray-based pncA genotyping of pyrazinamide-resistant strains of Mycobacterium tuberculosis. J. Med. Microbiol. 2005.54: 1127–31.

78. Trias.I, Jarlier. V, Benz.R, Porins in the cell wall of mycobacteria. Science. 1992; 258 (20):1479–81.

79. Plinke C, Walter K, Aly S, Ehlers S, Niemann S. Mycobacterium tuberculosisembB codon 306 mutations confer moderately increased resistance to ethambutol in vitro and in vivo. Antimicrob Agents Chemother. 2011;55:2891-6.

80. G. J. Alangaden, B. N. Kreiswirth, A. Aouad, M. Khetarpal, F. R. Igno, S. L. Moghazeh, and E. K. Manavathu. Mechanism of Resistance to Amikacin and Kanamycin in Mycobacterium tuberculosis. Antimicrob. Agents Chemother. 1998; 42(5): 1295–97.

81. C. E. Maus, B. B. Plikaytis, and T. M. Shinnick. Molecular Analysis of Cross-Resistance to Capreomycin , Kanamycin , Amikacin , and Viomycin in Mycobacterium tuberculosis. Antimicrob. Agents Chemother. 2005; 49(8): 3192–97.

82. A. Kru, P. Jureen, K. Levina, S. Ghebremichael, and S. Hoffner. Discordant Resistance to Kanamycin and Amikacin in Drug-Resistant Mycobacterium tuberculosis. Antimicrob. Agents Chemother. 2003; 47(9):2971–73.

83. Zhang Y. The magic bullets and tuberculosis drug targets. Annu Rev Pharmacol Toxicol. 2005;14:529–564

84. Cáceres NE, Harris NB, Wellehan JF, Feng Z, Kapur V, Barletta RG. Overexpression of the D-alanine racemase gene confers resistance to D-cycloserine in Mycobacterium smegmatis. Journal of Bacteriology. 1997;179(16):5046-5055.

85. Chen JM, Uplekar S, Gordon SV, Cole ST. A point mutation in cycA partially contributes to the D-cycloserine resistance trait of Mycobacterium bovis BCG vaccine strains. PLoS ONE. 2012;7(8): e43467:doi:10.1371/journal.pone.0043467.

86. Rengarajan, J., C. M. Sassetti, V. Naroditskaya, A. Sloutsky, B. R. Bloom, and E. J. Rubin. 2004. The folate pathway is a target for resistance to the drug para-aminosalicylic acid (PAS) in mycobacteria. Mol. Microbiol.2004; 53:275-282.

87. Zhao F, Wang XD, Erber LN, Luo M, Guo AZ, Yang SS, et al. Binding pocket alterations in dihydrofolate synthase confer resistance to para-aminosalicylic acid in clinical isolates of Mycobacterium tuberculosis. Antimicrob Agents Chemother. 2014;58:1479-87.

88. Mathys V, Wintjens R, Lefevre P, Bertout J, Singhal A, Kiass M, et al. Molecular genetics of para-aminosalicylic acid resistance in clinical isolates and spontaneous mutants of Mycobacterium tuberculosis. Antimicrob Agents Chemother. 2009;53 (5):2100-9.

89. Carette X, Blondiaux N, Willery E, et al. Structural activation of the transcriptional repressor EthR from Mycobacterium tuberculosis by single amino acid change mimicking natural and synthetic ligands. Nucleic Acids Research. 2012;40(7):3018-3030. doi:10.1093/nar/gkr1113.

90. DeBarber AE, Mdluli K, Bosman M, Bekker LG, Barry CE, III. Ethionamide activation and sensitivity in multidrug-resistant Mycobacterium tuberculosis. Proc Natl Acad Sci. 2000;97(17):9677-82.

91. Cholo MC, Steel HC, Fourie PB, Germishuizen WA, Anderson R. Clofazimine: current status and future prospects. J Antimicrob Chemother. 2012;67:290-8.

92. Hartkoorn RC, Uplekar S, Cole ST. Cross-resistance between clofazimine and bedaquiline through upregulation of MmpL5 in Mycobacterium tuberculosis. Antimicrob Agents Chemother. 2014;58(5):2979-81.

93. Hillemann D, Rüsch-Gerdes S, Richter E. In vitro-selected linezolid-resistant Mycobacterium tuberculosis mutants. Antimicrob Agents Chemother. 2008;52(2):800-1.

94. P. Beckert, D. Hillemann, T. a. Kohl, J. Kalinowski, E. Richter, S. Niemann, S. Feuerriegel. rplC T460C identified as a dominant mutation in linezolid-resistant Mycobacterium tuberculosis strains. Antimicrob. Agents Chemother. 2012; 56: 2743–45.

95. Escribano I, Rodriguez C, Llorca B, Garcia-Pachon E, Ruiz M, Royo G. Importance of the efflux pump systems in the resistance of Mycobacterium tuberculosis to Fluoroquinolones and linezolid. Chemotherapy. 2007;53(6):397–401
doi: 10.1159/000109769WOS:000251048900003.

96. World Health Organization. The use of bedaquinline in the treatment of multidrug-resistant tuberculosis. Interim policy guidance. World Health Organization Document. 2013;WHO/HTM/TB/2013.6:1-57.

97. Andries K, Verhasselt P, Guillemont J, Göhlmann HWH, Neefs JM, Winkler H, et al. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. Science. 2005;307:223-7.

98. Petrella S, Cambau E, Chauffour A, Andries K, Jarlier V, Sougakoff W. Genetic basis for natural and acquired resistance to the diarylquinoline R207910 in mycobacteria. Antimicrob Agents Chemother. 2006;50(8):2853-6.

99. Huitric E, Verhasselt P, Koul A, Andries K, Hoffner S, Andersson DI. Rates and mechanisms of resistance development in Mycobacterium tuberculosis to a novel diarylquinoline ATP synthase inhibitor. Antimicrob Agents Chemother. 2010;54(3):1022-8.

100. Paloion.J.C , Martin.A. Tuberculosis Clinical Trial Update and the Current Anti-Tuberculosis Drug Portfolio. Current Medicinal Chemistry, 2013, 20, 3785-3796 3785

101. Matsumoto M, Hashizume H, Tomishige T, et al. OPC-67683, a Nitro-Dihydro-Imidazooxazole Derivative with Promising Action against Tuberculosis In Vitro and In

Mice. Hopewell P, ed. PLoS Medicine. 2006;3(11):e466. doi:10.1371 /journal. pmed. 0030466

102. World Health Organization. Global tuberculosis report 2014. Geneva, Switzerland: WHO; 2014. WHO/HTM/TB/2014.08

103.World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. First edition. World Health Organization Document. 2006;WHO/HTM/TB/2006.361

104.Shah NS, Wright A, Bai GH, Barrera L, Boulahbal F, Martín-Casabona N, et al. Worldwide emergence of extensively drug-resistant tuberculosis. Emerg Infect Dis. 2007;13(3):380-7.

105. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008. World Health Organization Document. 2008;WHO/HTM/TB/2008.402:1-247.

106. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. 2011 update. World Health Organization Document. 2011; WHO/HTM/TB/2011.6:1-33.

107. World Health Organization. Systematic screening for active tuberculosis. Principles and recommendations. World Health Organization Document. 2013; WHO/HTM/TB/2013.04:1-133.

108. General statistics Office. Statistical Handbook of Vietnam. Hanoi: General Statistics Office, 2014, pp. 1–292.

109. Vietnam Ministry of Health, Health Partnership Group. Joint annual health review 2014, Strengthening prevention and control of non-communicable disease. Hanoi, 2015.pp.1-328

110. Vietnam Ministry of Health, Health Partnership Group. Joint annual health review 2011: Strengthening management capacity and reforming health financing to implement the five-year health sector plan 2011–2015. Hanoi, 2011.pp.1-220

111. Vietnam Ministry of Health, Health Partnership Group. Joint annual health review 2012: Improving quality of medical services. Hanoi, 2012.pp.1-203

112. Vietnam Ministry of Health and Health Partnership Group. Vietnam joint annual health review 2013: Towards Universal Health Coverage. Hanoi, 2013.pp.1-215

113. Vietnam Ministry of Health. Five-Year Health Sector Development Plan 2011-2015. Vietnam Ministry of Health.Hanoi, 2011.pp.1-51

114. Vietnam Ministry of Health. Report for HIV/AIDS control porgramme by 30/9/2014. Vietnam Ministry of Health.Hanoi, 2014. Ref Type: Report.

115. Joint United Nations Programme on HIV/AIDS (UNAIDS), "GLOBAL REPORT: UNAIDS report on the global AIDS epidemic 2013, UNAIDS 2013. Ref Type: Report.

116. Dye C, Maher D, Weil D, Espinal M, Raviglione M. Targets for global tuberculosis control. Int J Tuberc Lung Dis. 2006;10:460-2.

117. Huong N T, Duong B D, Co N V, Quy H T, Tung L B, Bosman M, a Gebhardt, J. P. Velema, J. F. Broekmans, M. W. Borgdorff. Establishment and development of the National Tuberculosis Control Programme in Vietnam.Int J Tuberc Lung Dis 2005;9 (2):151-6.

118. Dye C, Garnett GP, Sleeman K, Williams BG. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Lancet. 1998;352:1886-91.

119. Vree M, Duong B D, Co N V, Borgdorff M W, Cobelens F G J.Tuberculosis trends, Vietnam.(Correspondence).Emerg Infect Dis 2007;13(5):796-7.

120.Nhung. N. V, Hoa.N. B, Sy.D. N, Hennig.C. M, Dean.A. S. The Fourth National Anti-Tuberculosis Drug Resistance Survey in Viet Nam. Int J tuber Lung dis. 2015; 19(6): 670–5

121. National Tuberculosis Program Vietnam. Application to the GLC for access to second-line anti- tuberculosis drugs in the framework of the programmatic management of drug-resistant tuberculosis, Hanoi: National Tuberculosis Control Programme of Vietnam; 2007

122. National Tuberculosis Control Program of Vietnam. National Guidelines for Programmatic   Management of Drug Resistance Tuberculosis. Hanoi: Ministry of Health; 2009: 1-142.

123. National Tuberculosis Control Program of Vietnam. Public private mixed in TB control, NTP update data. Hanoi: National Tuberculosis Control Program of Vietnam. 2015; Ref Type: Report.

124. Pandey S, Quelapio M, Hennig C, Khanh PH. Green Light Committee Monitoring Mission Report for Vietnam. The Philippines: World Health Organization -Western Pacific Regional Office; 2013: 1-73

125. National Tuberculosis Control Program of Vietnam. National Guidelines for quality control of culture laboratory in Vietnam. Hanoi National Tuberculosis Control Program of Vietnam; 2012: 1-19.

126. National Tuberculosis Control Program of Vietnam. Mid-term development plan for TB control programme of Vietnam, 2007- 2011, Hanoi: National Tuberculosis Control Programme of Vietnam; 2006

127. National Tuberculosis Control Program of Vietnam. Mid-term development plan for TB control programme of Vietnam, 2011- 2015, Hanoi: National Tuberculosis Control Programme of Vietnam; 2010: 1-125

128. National Tuberculosis Control Program of Vietnam. Annual review meeting report of the National TB Control Programme of Vietnam, 2009-2014. Hanoi: National Tuberculosis Control Programme of Vietnam; Ref Type: Report.

129. National Tuberculosis Control Program of Vietnam. Human resource development for TB Control Programme of Vietnam, 2007-2011. Hanoi: National Tuberculosis Control Programme of Vietnam; 2011. Ref Type: Report.

130. The Global Fund to Fight AIDS, Tuberculosis and Malaria. Monitoring and Evaluation Toolkit, Edition 4. November. 2011

Chapter 2. ASSESSMENT FOR MULTIDRUG RESISTANT TUBERCULOSIS CONTROL POLICIES AND PRACTICES IN VIET NAM, WITH A SPECIAL FOCUS ON CASE FINDING STRATEGIES

Hoang Thi Thanh Thuy[1*], *corresponding author; Email: hoangthanht@gmail.com

Nguyen Viet Nhung[1], Email: vietnhung@yahoo.com

Dinh Ngoc Sy[2], Email: syminhquan@gmail.com

Nguyen Binh Hoa[1,3], Email:nguyenbinhhoatb@yahoo.com

Frank Cobelens[4], Email: f.cobelens@amc-cpcd.org

Guy Thwaites[5,6] Email: gthwaites@oucru.org

Nguyen Thu Anh[7], Email: thuanh.nguyen@sydney.edu.au

Pham Huyen Khanh[8], Email: phamh@wpro.who.int

Heiman F.L. Wertheim[6,9,10] Email: heiman.wertheim@gmail.com

1. National Tuberculosis Control Program of Viet Nam- National Lung Hospital (VNTP-NLH)
2. Viet Nam Association for Tuberculosis and Lung Disease, Hanoi, Viet Nam
3. Centre for Operational Research, International Union Against Tuberculosis and Lung Disease, Paris, France
4. Department of Global Health and Amsterdam Institute for Global Health and Development, Academic Medical Center, Amsterdam, Netherlands
5. Wellcome Trust Major Overseas Program, Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam
6. Nuffield Department of Clinical Medicine, Centre for Tropical Medicine, University of Oxford, United Kingdom.
7. Woolcock Institute Of Medical Research, Australia
8. Office of the WHO Representative in Viet Nam
9. Wellcome Trust Major Overseas Program, Oxford University Clinical Research Unit, Hanoi, Viet Nam (OUCRU)
10. Department of Medical Microbiology, Radboudumc, Nijmegen, Netherlands

2.1 Background

Multidrug resistant TB (MDR-TB) is a major public health concern that posed the challenges to the effective TB control programme globally. The disease is caused by the emergence of strains that are resistant to the most important anti TB drugs including rifampicin and isoniazid. This occurs when antibiotics are improperly used for drug-susceptible TB patients, poor drugs supply and also caused by transmission of bacteria in the community[1][2]. In 2013, there were 480,000 people developed MDR-TB in the world[3].

After the first WHO guideline for Programmatic Management of Drug Resistant Tuberculosis (PMDT) in 2006, management of drug resistant TB in Viet Nam started to gain attention. As a result, the management of MDR-TB has been included in the national TB control program since 2007 with several policies and guidelines being developed to strengthen the management of MDR-TB in the country. Funding for the PMDT has increased over time, with investments from both government and international donors reaching nearly 8,000,000 USD in 2015.

The first pilot of the PMDT was piloted in 2009 in Ho Chi Minh city in a cohort of 100 MDR-TB patients with a treatment success rate of 73%. From 2010 onwards, the PMDT has gradually expanded its coverage to 45 provinces in 2015, with PMDT policies being updated over time in line with newly released WHO guidelines and contextualized to Viet Nam. Along with policy changes, Viet Nam has continuously increased the number of MDR-TB patients with a treatment success rate of approximately 70%, higher than other low and middle income countries (LMIC) with rates from 44-58%[3][4][5].

The number of 948 MDR-TB cases detected and treated annually under the existing PMDT, however, far fall short of the total estimated number of MDR-TB cases of 5,100 [3]. Before expanding PMDT coverage, an assessment of the current MDR-TB policy and practices is needed to come with recommendations to improve MDR-TB control. A systematic review illustrated that important gaps and discrepancies exist for many countries in their MDR-TB guidelines measured against WHO-recommended interventions for PMDT[6]. In this chapter the MDR-TB control policies and practices in Viet Nam with a special focus on case-detection are evaluated. We also assess how MDR-TB control policies in Viet Nam have developed over time in response to updates in WHO guidelines.

2.2 Methods

We conducted a review of key policies, guidelines and reports related to the PMDT, the development process of guidelines and operational documents for PMDT in Viet Nam. To assess PMDT policy development and implementation we did systematic interviews of key informers of TB health staff at both central and provincial levels. Furthermore, PDMT performance was assessed by analyzing selected indicators using the Monitoring and Evaluation Toolkit from Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM, table 2-1).

Reviewed policies, guidelines and reports included: (i) WHO guidelines for PMDT from 2008-2014, (ii) national PMDT guidelines of Viet Nam developed by the National Tuberculosis Control Programme (NTP) to specify the case finding and treatment strategy for drug resistant TB (iii) standard operational procedures (SOPs) for PMDT (iv) official letters by the NTP to inform policy changes during PMDT implementation, and (v) annual progress reports of the NTP. The PMDT guidelines and operational documents for PMDT in Viet Nam were compared to those developed by WHO by each topic to assess the comprehensiveness and timeliness. Dates of publications were recorded to allow for assessing chronology of policy changes. In case of discrepancies, reasons for these were sought for in the documents or through contacting involved policy makers.

Indicators for both diagnosis and treatment of MDR-TB are used in this study to assess the implemented policies. Seven indicators developed by GFATM in collaboration with WHO's Global TB Programme and the Stop TB Partnership were used, including: diagnosis, enrollment, treatment outcome and supply management for MDR-TB[7]. Data to construct these indicators were collected from the routine surveillance system of the NTP from 2009-2015. All PMDT provinces provide quarterly reports to the NTP of the tested presumptive MDR-TB cases (individuals considered at high risk for MDR- TB) per different risk categories, number of notified MDR-TB cases, the number of MDR-TB patients enrolled on treatment, culture conversion at six months, and stock on hand of anti-TB drugs. Treatment success rate was reported annually and is defined as the proportion of patients started on treatment who had cure or treatment completed as the outcome. Quality assurance for drug

susceptibility testing was assessed by proficiency testing conducted by Institute of Medical and Veterinary Science (IMVS), Adelaide, Australia on a yearly basis.

Table 2-1. PMDT Indicators recommended by GFATM (in collaboration with WHO's Global TB Programme and the Stop TB Partnership) and adoption status by the Viet Nam PMDT

	Indicator	Category
1	Quality assurance for drug susceptibility testing. *Definition*: Laboratories showing at least 90 percent proficiency for isoniazid and rifampicin drug susceptibility testing among the total number of laboratories that undertake drug susceptibility testing during the reporting period (number and percentage).	Improving diagnosis
2	Number of TB cases with result for drug susceptibility testing. *Definition:* Number of TB cases with results for diagnostic drug susceptibility testing for MDR-TB among those eligible for drug susceptibility testing according to national policy during the specified period of assessment (number and percentage)	Detection
3	Number of confirmed MDR-TB cases enrolled on MDR-TB treatment regimen. *Definition:* Number of laboratory-confirmed MDR-TB cases enrolled on second-line anti-TB treatment during the specified period of assessment (number)	Enrollment
4	Delay in start of MDR-TB treatment. *Definition:* The duration in days between the date of MDR confirmation (DST results showing resistance to both isoniazid and rifampicin in the MDR-treatment register) and the date when the patient started a prescribed second-line drug regimen as per the MDR-treatment register.	Enrollment
5	Culture conversion at six months.	Interim results

	Definition: MDR-TB cases initiated on a second-line anti-TB treatment who have a negative culture at the end of six months of treatment during the specified period of assessment (number and percentage)	
6	Treatment success rate. *Definition:* Laboratory-confirmed MDR-TB cases successfully treated (cured plus completed treatment) among those enrolled in second-line anti-TB treatment during the year of assessment (number and percentage)	Final outcome
7	Reporting units with stock-outs of first-line and second-line anti-TB drugs. *Definition:* Reporting units (districts or basic management units) reporting no stock-out of second-line anti-TB drugs on the last day of the quarter (number and percentage)	Procurement and supply management

2.3.Results

2.3.1 Development and dissemination of guidelines and operational documents for PMDT

In this study, we reviewed all guidelines for PMDT developed by WHO in 2008, 2011 and 2014. The WHO guidelines were compared to the following documents of the Viet Nam PMDT: Viet Nam PMDT 2009 guidelines, PMDT SOPs published in 2012, and all reports and official letters issued by the NTP to inform policy changes during 2009-2015. The national mid-term plan for TB program for the period 2007-2011 and 2011-2015 were also reviewed. Key findings are presented below.

Management of MDR-TB was included for the first time in the mid-term plan of the National TB Control Program (NTP) in the period 2007-2011 as one among six objectives for TB control[8]. A task force on MDR-TB was established with support from KNCV Tuberculosis Foundation to develop a plan for PMDT implementation in the period 2007-2011[9]. The plan was approved by Green Light Committee (GLC) in 2007and funded by the GFATM to pilot in Ho Chi Minh city and expanded to other sites.

In 2009, when the PMDT started, the first national guideline for PMDT was published based on the 2008 WHO guidelines[10]. A Committee was formed by the NTP to develop this guideline. The development of this guideline involved NTP staff from central levels, TB doctors from Pham Ngoc Thach hospital who were in charge of supervision of Southern provinces, and technical consultants (from Royal Netherlands Tuberculosis Foundation- KNCV) for review and comments. The NTP coordinators played a role of secretariat and prepared the draft version of the guidelines. The guideline was contextualized to Viet Nam which was based on the five components of the DOTS strategy and limited diagnosis and treatment capacity of the NTP system. Priority was given to the highest risk groups for screening, and an ambulatory model of care for case management after patients discharged from hospitalization was utilized. It was approved by the NTP executive board in 2009 and disseminated to the TB units in the same year.

To ensure consistency during implementation among all PMDT sites, a draft SOP was developed and piloted in Pham Ngoc Thach hospital, Ho Chi Minh city. Results of the pilot was used to develop a standardized SOP for management of TB patients nationwide[11]. The SOPs were endorsed by the NTP in 2012 and printed and distributed to all implementing sites. This set of SOPs consisted of nine operational and· technical documents including (a) procedures for diagnosis of drug resistant TB accompanied by the procedure for using Xpert MTB/RIF; (b) sputum collection, storage and transportation; (c) consultation, registration and management for MDR-TB patients; (d) patient referral from district TB unit to treatment center; (e) treatment for MDR-TB patients at treatment unit in hospitalization phase; (g) adverse drug reactions management and reporting during MDR-TB treatment; (h) patient referral from treatment center to district TB units; (i) treatment, monitoring and management of outpatients; and (k) drug management for MDR-TB patients.

During the period 2009-2015, the PMDT policies in Viet Nam for case finding and treatment strategy were updated to follow the revisions of the WHO guidelines of 2011 and 2014. Approved changes were disseminated through 17 instruction letters from the central level to the provincial and district TB units over 2009 – 2013 and through yearly PMDT training courses. All PMDT sites were trained annually on general management of PMDT, clinical management of MDR-TB, recording and reporting, and laboratory performance. In 2013, interviews with TB staff at PMDT sites using an interview guide were conducted privately to investigate about

training provided to staff, their knowledge and awareness about PMDT. Reports from each interview were made and these revealed that the policy changes were not understood clearly due to lack of awareness about the updated policy and lack of standardized PMDT training modules [12]. To address this issue, the NTP revised the SOPs in 2014 and developed standard PMDT training modules, conducted more trainings and supervisions to all levels, and strengthened the communication by utilization of teleconferences to discuss about policy changes and consultation for clinical management.

In 2011, the mid-term plan for the NTP for the period 2011-2015 was developed and approved by Ministry of Health (MOH), which included PMDT as important component[13]. This plan was consolidated with other health programs to form a targeted national health program with secured funding approved by the Prime Minister in 2012. In the national health program, it is the goal to control the transmission of MDR-TB and increase the access for the population to MDR-TB management services from 25% in 2011 to 55% in 2015[13]. In January 2014, MDR-TB was emphasized in a resolution adopted by the Prime Minister to strengthen the implementation of activities towards reaching the Millennium Development Goals (MDGs)[14]. For the attainment of stronger political commitment for TB control, the National Strategic Plan for the NTP towards 2020 and vision to 2030 was approved by the Deputy Prime Minister in March 2014. Comprehensive solutions were set to achieve the set goal including policy, advocacy, technical and financial solutions. It was expected that the NTP will keep MDR-TB under control at the rate of 5% among new TB cases along with policies to monitor the trend of MDR-TB and TB-drugs adverse reactions[15].

2.3.2 Case finding strategy and policy changes over time

Case finding for drug-resistant TB is the process for identifying MDR-TB presumptive patients (individuals considered at high risk for MDR- TB) to diagnosing and reporting MDR-TB cases detected. Eight components of case finding strategy are assessed: (1) targeting risk groups, (2) strategies for the use of Drug Susceptibility Testing (DST), (3) use of second-line susceptibility testing, (4) management of specimens and results, (5) case finding in pediatric patients, (6) case finding in HIV infected patients, (7) case-finding of patients with mono- and poly-drug resistance, and (8) case finding for extra-pulmonary tuberculosis. Comparisons of the WHO and

Viet Nam Guidelines of MDR-TB case finding strategies are presented in table 2-2. The WHO guidelines of 2008, 2011, and 2014 are compared with the Viet Nam policies in 2009-2011, 2012-2013, and 2014-2015, respectively because it took at least one year for Viet Nam to develop and revise the policies after the three WHO publications. Table 2-2 illustrates that since 2008, the WHO guidelines include a wide range of risk groups, recommend rapid DST with molecular tests and second line DST to diagnose XDR-TB. However, Viet Nam did not immediately adopt all WHO recommendations (Table 2-2). Due to limited resources, Viet Nam could only focus on a limited number of risk groups that gradually expanded since implementation of Xpert MTB/RIF testing.

Table 2-2. Comparison of the WHO and Viet Nam Guidelines of MDR-TB case finding strategies

Guidelines contents		WHO2008 /VN 2009-2011	WHO 2011 /VN 2012-2013	WHO 2014 /VN 2014-2015
Targeting risk groups	WHO	All risk groups for DR-TB are mentioned. More attention to contact investigation.	No update	No update
	VN	Mainly focus on limited number of very high risk groups	Stepwise extending to include more risk groups	-Guidelines for contact management -Screening among new cases in some provinces in 2014
Strategies for the use of DST	WHO	Strong encouragement of DST for all patients with increased risk for MDR-TB More emphasis on the role of rapid test for early case detection	Rapid test is recommended over conventional DST	Update for interpretation of rapid test result
	VN	Hain test (Line probe assay to detect rifampicin and isoniazid resistance) .and conventional DST were used	Use Xpert MTB/RIF more widely as the screening test while using Hain test less among MDR-TB risk groups	Update the interpretation of Xpert MTB/RIF in 2014
Use of second-line susceptibility testing (SL DST)	WHO	SL DST to MDR-TB patients at increased risk for XDR-TB	SL DST to all MDR-TB patients	Conventional DST is recommended
	VN	Only for non-converters* after six months of MDR-TB treatment	Include some more categories of patients** to be tested from 2013	-Additional for close contacts of XDR-TB patients in 2014 - Stepwise to give SL DST to all rifampicin resistance from 2015
Case finding in pediatric patients	WHO	Tuberculin test, smear, chest Xray, culture and DST are recommended. TB can be clinically diagnosed without bacteriological evidence.	The use of rapid test is recommended	Children with a single Xpert MTB/RIF-negative should have further diagnostic testing
	VN	Mentioned in guidelines, but not in practice	Started to use Xpert MTB/RIF for TB and DR-TB diagnosis in	Update guideline for diagnosis in children when XpertMTB/RIF-

				children	negative in 2014
Case finding in HIV infected patients	WHO	DST at the start of TB treatment in all HIV patients Use rapid diagnostic techniques if possible Implement XDR-TB diagnosis in high prevalent setting	Rapid test is recommended over conventional DST	Stronger emphasis on the role of rapid test to detect rifampicin resistance and the need of SL DST for XDR-TB diagnosis	
	VN	Mentioned in guidelines, but not in practice	Started to use Xpert MTB/RIF for TB and DR-TB diagnosis in HIV infected patients	XDR TB diagnosis for MDR-TB or rifampicin resistance with HIV from 2015	
Case-finding of patients with mono- and poly- drug resistance	WHO	Recommended strategies to detect mono and poly resistant TB during the course of MDR-TB diagnosis	Rapid DST followed by further DST and clinical evaluation	No update	
	VN	Not available	Rifampicin resistance diagnosed by Gene Xpert MTB/RIF	Rifampicin resistance separate from MDR TB by further Hain testing among rifampicin resistance from 2015	
Case finding for extra Pulmonary tuberculosis (EPTB-MDR- TB)	WHO	Not clearly developed	Not clearly developed	EPTB-DR can be diagnosed by Xpert MTB/RIF or conventional DST	
	VN	Not available	Not available	Start to use Xpert MTB/RIF in non-respiratory specimens	

* People whose sputum culture had not converted from positive to negative

** Including retreatment cases (relapse or treatment failure), treatment after default, HIV positive TB patients, household contacts of MDR-TB cases, and TB presumptive patients with a history of TB drug use for more than 1 month.

Targeting risk groups

The WHO Guideline of 2008 identified the following risk groups for MDR-TB: retreatment patients, close contacts of known MDR-TB patients, patients who remain smear positive at month 2 or 3 of short-course chemotherapy with first line anti-TB drugs, people who were in an institution with high risk of MDR-TB, individuals infected with HIV. It was recommended for

each country to identify the risk groups based on patient's history and epidemiological data of drug resistance in the country. Intensive investigations of contacts with MDR-TB and especially XDR –TB cases should be conducted to increase early detection of MDR-TB cases. Viet Nam had no data available on drug resistance for the different patient groups, and as a result it was decided for the 2009 PMDT guideline to include all WHO recommended risk groups. However, only patients with a history of treatment such as failure cases, non-converters of the retreatment regimen and chronic cases were given priority in Viet Nam and the remaining categories were ignored due to limited resources. Management of MDR-TB contacts was not established yet at the time. MDR-TB contacts were advised to self-refer for TB testing in case of symptoms suggesting TB.

From 2012, with the introduction of Xpert MTB/RIF in Viet Nam, additional risk groups for MDR-TB screening were included: retreatment cases (relapse or treatment failure), treatment after loss to follow-up for more than two months, HIV positive TB patients, household contacts of MDR-TB cases, and TB presumptive patients with a history of TB drug use for more than 1 month. Despite this expansion of risk groups, many presumptive MDR patients were missed for screening until 2013 (refer to indicators for PMDT performance for more detail).

In 2014, Viet Nam revised the PMDT guideline according to the WHO Companion Hand Book. Contact management was also incorporated where symptomatic contacts of MDR-TB would be registered, followed up and evaluated by health staff systematically. Since 2015, in addition to the risk group expansion, Viet Nam will also start to screen for MDR-TB among new smear-positive TB cases (started in 14 provinces with high burden of MDR-TB).

Strategy for drug susceptibility testing (DST)

The second version of WHO guidelines (2008) recommends performing DST for at least isoniazid and rifampicin for all patients at increased risk for MDR-TB. However, patients from very high risk groups (for example failures of retreatment regimen or chronic cases) are allowed to be enrolled to MDR-TB treatment without DST if resources for DST are limited. From 2009 to 2011, rapid tests (Line probe assay -LPA, Hain test) were used to diagnose MDR-TB among failure cases of first-line treatment and for non-converters (after 3 months) of retreatment cases. Failure of retreatment cases and chronic cases were put on MDR-TB treatment without Hain test.

The third WHO guidelines in 2011 recommended the use of rapid molecular DST rather than conventional testing or no testing. From 2012, Xpert MTB/RIF was expanded to replace Hain tests in Viet Nam. Xpert MTB/RIF is currently used widely as the first screening test to detect rifampicin resistance for all PMDT sites. The Hain test is only used at the National Reference laboratory and Pham Ngoc Thach hospital, mainly for patients who self referred for TB diagnosis.

The fourth WHO guidelines in 2014 updated the interpretation of molecular test results accounting for the patient risk category. According to this recommendation, if the Xpert MTB/RIF assay detects rifampicin resistant TB in patients considered at high risk for MDR-TB, no confirmatory testing needs to be performed. This is because for these cases the positive predictive value for RIF resistance is considered sufficiently high[16]. Only in low risk individuals, confirmatory testing is recommended using another phenotypic or another genotypic test. Further DST for isoniazid and second line drugs is recommended to adjust the empirical second line treatment regimen according to the DST results. Viet Nam requires confirmatory testing if rifampicin resistance is detected among low risk groups. However until 2014, due to limited resource, no further DST was provided prior to treatment. Patients will be tested for second line TB drugs only if their sputum does not convert after 4 months of MDR-TB treatment. From 2015, the NTP plans to stepwise manage XDR TB and use Hain test for first line drugs and DST for second line drugs to patients with rifampicin resistant TB detected by Xpert MTB/RIF.

Use of second line DST in case-finding and diagnosing XDR-TB

As per the second WHO guidelines of 2008, patients at risk for XDR-TB or at risk for failure of MDR-TB treatment should receive DST for injectable agents and fluoroquinolones. Those at risk are: failure of MDR-TB treatment, close contact of XDR-TB or contact of patients who failed from MDR-TB treatment, patients who have evidence of progressive disease after 4 months of second-line treatment, patients having persistent positive smear or culture after 8 months or more of treatment. For XDR-TB in a high prevalence setting, second line drug (SLD) DST may be used for all MDR-TB who are HIV positive. The third WHO guidelines (2011) and the Companion Handbook (2014) recommended using second line DST for all MDR-TB patients, or at least for patients with risk factors for XDR-TB. In Viet Nam, from 2009-2012, without

experience and capacity for XDR-TB diagnosis and treatment, the policy for this period was only to perform DST for patients whose sputum did not convert after six months of MDR-TB treatment. This policy was intended to monitor XDR-TB as no drugs for XDR-TB treatment were available at the time. From 2013, with the improvement in technical capacity to perform second line DST, more categories of patients were added for testing including (i) rifampicin resistance with previous SLD use, (ii) MDR-TB treatment non-converters, and (iii) random 10% of rifampicin resistant cases, even though still no treatment for XDR-TB was available. Since 2014, Viet Nam included close contacts of XDR-TB patients for testing. Currently, Viet Nam performs DST for second line drugs: kanamycin, capreomycin, amikacin and ofloxacin. As of 2015, it is Viet Nam NTP policy to start managing and providing treatment for XDR-TB at small scale (three provinces: Ha Noi, Ho Chi Minh City, and Can Tho) to draw lesson learned, and later on to expand to the rest of the country.

Case finding in pediatric patients

The second WHO guideline recommended using tuberculin testing, sputum smear examination, chest X-ray, culture and DST for MDR-TB diagnosis in children. Children with TB suggestive symptoms who are close contacts of MDR-TB patients can already start MDR-TB treatment even if they are smear and culture negative. This strategy for children is mentioned in the Vietnamese guidelines but was not put into practice until 2009 due to limited diagnostic capacity for culture and DST and absence of mechanisms of managing contacts. Since 2012, Xpert MTB/RIF has been used in Viet Nam to detect TB and rifampicin resistance TB in children with TB presumptive and/or at increased risk for MDR-TB in line with WHO guidelines from 2011.

Case finding in HIV infected patients

The second WHO guideline (2008) recommends that DST (either rapid or conventional) should be performed at the start of TB treatment in HIV co-infected patients. Patients can be enrolled into MDR-TB treatment empirically without DST confirmation. The Companion Hand Book recommends that all TB-HIV co-infected patients, besides rapid DSTtest, should also be tested for second-line anti-TB drug resistance in case of DR-TB. Similar to the policy for MDR-TB case finding in children, DST for TB-HIV patients is mentioned in the PMDT guidelines of Viet Nam since 2009[10]. However it was not implemented between 2009-2011 due to limitations in

diagnostic capacity for culture and DST. Although there was no policy to provide DST for HIV infected patients in this period, HIV testing was provided to TB and MDR-TB patients in Viet Nam. The indicator set by the NTP for the period 2013-2015 is to provide HIV tests for 65% to 90% of all TB patients. This indicator was set for HIV testing among TB patients in general and did not prioritize patients with presumptive MDR-TB. Until 2014, 72.5 % of TB patients were tested for HIV[17]. From 2012, Viet Nam started to use Xpert MTB/RIF to detect rifampicin resistance in HIV infected patients. However, second line DST is not yet performed when rifampicin resistance is detected due to limited capacity for diagnosis and treatment of XDR-TB.

Case-finding of patients with mono- and poly-drug resistance

In 2008, WHO recommended to identify cases of mono- and poly-drug resistance (resistance to one or more anti-tuberculosis drugs but not to both isoniazid and rifampicin) by DST. Due to limited resources for diagnosis and treatment of DR-TB, it was NTP's policy in the period 2009-2011 to focus on MDR-TB only.

The NTP uses Xpert MTB/RIF since 2012 to detect rifampicin resistant TB. However, isoniazid susceptibility testing is not performed in rifampicin resistant TB due to limited resources. As of 2015, it is the NTP policy to provide the Hain test to detect isoniazid resistance in rifampicin resistance cases detected by Xpert MTB/RIF. Additionally, if rifampicin resistance is not detected among patients who failed or relapsed from retreatment regimen, conventional DST to four first line drugs including streptomycin, isoniazid, rifampicin, etambutol (SIRE) will be performed to detect mono or poly resistance.

Drug-resistant TB case finding among extra-pulmonary TB

Until the second and the third WHO guidelines in 2008, 2011, case finding for extra-pulmonary (EPTB) MDR-TB has not been clearly developed. The Companion Hand Book (2014) recommends that drug-resistant extra-pulmonary TB can be diagnosed by Xpert MTB/RIF or conventional DST. To diagnose meningitis rapidly, it is recommended to use Xpert MTB/RIF in cerebrospinal fluid specimens due to the severity disease in these patients. Therefore in 2014, Viet Nam updated their guideline to also use Xpert MTB/RIF in non-respiratory specimens to diagnose EPTB, particularly TB meningitis.

2.3.3 PMDT performance

Six among the seven indicators to monitor MDR-TB programs developed by the GFATM have been adopted by Viet Nam over time. At the start few indicators were adopted due to time constraints and lack of an adequate health management information system. Currently only one indicator (delay in start of MDR-TB treatment) has not been adopted due to time constrains. PMDT indicators achieved during the period 2009-mid 2015 are presented in the table 2-3 below.

Table 2-3. Measurements of PMDT indicators for performance framework (PF)

from 2009-2015

	Indicators		2009	2010	2011	2012	2013	2014	Mid-2015
1	Quality assurance for drug susceptibility testing	Target (%)	100	100	100	100	100	100	100
		Achievement (%)	100	100	100	100	100	NA	NA
2	% of presumptive MDR-TB patients with result for isoniazid and rifampicin susceptibility testing*	Target (%)	Not set	Not set	Not set	Not set	28	40	55
		Achievement (%)	NA	NA	14.4	20.4	31.2	82.5	NA
3	Confirmed MDR-TB cases enrolled on MDR-TB treatment regimen	Target (number)	100	250	698	900	916	1502	2200
		Achievement Number (%)	101 (101)	97 (39.8)	578 (82.8)	713 (79.2)	943 (102.9)	1532 (102)	NA
4	MDR-TB cases on MDR-TB treatment regimen with negative culture by six months	Target (%)	NA	NA	65	70	75	75	75
		Achievement (%)	77	75	73	74	57	67	NA
5	Treatment success rate	Target (%)	75	75	75	75	75	75	75
		Achievement (%)	73	78	72	70	NA	NA	NA
6	Reporting units with no stock-outs of first-line and second-line anti-TB drugs:	Target (%)	Not set	Not set	Not set	Not set	100	100	100
		Achievement (%)	100	100	**	**	100	100	NA

(*)Xpert MTB/RIF is used since 2012 to replace Hain test, so INH susceptibility results were not available for this indicator from 2012.

(**) stock out reported, no exact numbers known; (NA): not available

The first indicator on quality assurance shows that between 2009-2013, two reference laboratories participated in DST proficiency testing and had an optimal score. Proficiency testing was not done in 2014 due to renovations.

The second indicator determining the proportion of presumptive MDR-TB patients that have a DST result was not included in the monitoring and evaluation plan until 2013. Data to calculate this indicator was available since 2011 and showed that the proportion of patients with DST performed increased from 14% in 2011 to 85% in 2014. The steep rise was mainly due to the introduction of Xpert MTB/RIF rapid test system.

The third indicator is to measure the number of confirmed MDR-TB cases enrolled in MDR-TB treatment regimen. The performance showed a favorable achievement compared with the target except for 2010 due to a delay in the drug supply.

The fourth indicator to evaluate how many MDR-TB cases have converted to negative culture after six months of treatment has been included in the monitoring plan since 2011. The data was already collected by the NTP since 2009 to evaluate patient's response to treatment. Between 2009 and 2012, 75% of MDR-TB patients culture converted by six months of treatment. It decreased to 57% and 67% for a cohort of patients in 2013 and 2014.

The fifth indicator for MDR-TB treatment success rate is evaluated 48 months after start of treatment. The target for this indicator was set to the WHO target of 75% for treatment success. Viet Nam achieved 73% and 78% of patients treated successfully between 2009 and 2010. However, the outcome of cohort 2011 and 2012 showed a decreased to 72% and 70%.

The sixth indicator concerns the drug supply to ensure treatment for MDR-TB patients. It was not included in the monitoring plan between 2009 and 2010. Available reports do show that no stock outs occurred in this period. Between 2011 and 2012, stock outs of SLDs were reported by several sites, but no details are available. Since 2013 no stock outs of SLD have been reported.

2.4. Discussion and recommendations

In general the development process of guidelines and operational documents for PMDT in Viet Nam goes through a process of problem identification, stakeholder involvement, consideration of resources, an official approval and subsequent delivery of policy documentation to implementing

sites. There is a considerable delay in the development of SOPs which took three years since implementing PMDT.

Most WHO recommended MDR TB risk groups are included for screening in Viet Nam policies. Since 2013, 35 provinces with the highest number of MDR-TB, accounting for approximately 85% of all MDR-TB for the whole country, are covered by PMDT. Untill 2013 the proportion of MDR TB presumptive tested (indicator 2) accounted for about 30%, and increased to 85% in 2014 to cover eligible presumptive MDR-TB cases as per national guidelines. This increase can be explained by an improved training and communication strategy for PMDT in 2014 based on an assessment in 2013 (submitted for publication).

Screening new smear positive TB cases for MDR-TB is one way to increase the MDR-TB case detection rate and in line with the global strategy of testing in new TB cases[18]. However this is too costly as it is currently estimated that the proportion of MDR-TB among new TB cases is approximately 4%, and 23% among previously treated TB cases in Viet Nam [3]. Therefore, as far as new TB cases are concerned, Viet Nam will target high risk groups for MDR-TB, including new TB cases in institutions with high risk of MDR-TB such as prisons and hospitals. In order to manage contacts of MDR-TB cases systematically, Viet Nam willfollow contacts more closely to early MDR-TB diagnoseand exclude them from chemoprophylaxis as offered to contacts of susceptible TB cases[1]. It is desirable for the PMDT to have better epidemiological data on MDR-TB by risk groups and by geography to target case finding and make better use of limited resources in the future.

Viet Nam has continuously followed the most updated versions of WHO TB policy changes. Viet Nam introduced Xpert MTB/RIF to test presumptive MDR-TB cases one year after the WHO recommendation (2011), and now also uses this test to diagnose extra-pulmonary DR-TB. For detection of mono and poly resistance to drugs other than rifampicin in a limited resource setting, it is appropriate to use conventional DST among patients who were previously treated with the retreatment regimen but are not resistant to rifampicin as detected by Xpert MTB/RIF. Given that the MDR-TB rate in Viet Nam is about 80% among failure cases [19]and that Xpert MTB/RIF has only 95% sensitivity[16], it would be beneficial to start these patient on empirical MDR-TB treatment awaiting phenotypic DST results. In order to detect more mono and poly

drug resistance, Viet Nam should consider performing first line DST in any TB patient who has been previously treated but has no resistance to rifampicin by Xpert MTB/RIF. There is a high proportion of resistance to drugs other than rifampicin in Viet Nam: 44.2% for streptomycin and 44.7% for isoniazid among previously treated patients[20]. Treatment of undetected mono and poly resistant TB patients using standardized short-course chemotherapy can increase the risk of further acquired resistance including MDR-TB, and thus needs to be avoided[1][2]. Viet Nam is therefore recommended to detect to mono and poly drug resistant TB properly and for resistant cases provide treatment with modified SCC or even second line drugs to prevent drug resistance amplification[2].

Susceptibility testing for isoniazid, fluoroquinolones and second-line injectable drugs is not performed on rifampicin resistant TB isolates to direct treatment. Not doing this may result in that the potent drug isoniazid is not administered to about 5% (or even higher if we take into account low-level INH resistance) of patients with TB resistant to rifampicin but susceptible to isoniazid[20]. SLD DST is needed to provide appropriate treatment to XDR-TB patients and patients who have fluoroquinolone resistant strains which are estimated to comprise 5.6% and 16.7% of MDR-TB patients in Viet Nam, respectively, according to a preliminary report from a TB drug resistance survey conducted in 2011-2012 (unpublished data). It is expected that as of 2015 Hain testing for first line drugs and SLD DST will be introduced in a stepwise manner for all rifampicin resistant strains detected by Xpert MTB RIF.

Regarding case-finding and diagnosing XDR-TB, due to limited capacity and experience in XDR-TB treatment, the policy of using second-line DST to diagnose XDR-TB is only intended for monitoring and evaluation and not for treatment, which is clearly undesirable. Fortunately, this issue will be addressed as of 2015. As susceptibility to older and newer generation fluoroquinolones varies[2], it is recommended to perform DST specifically for the fluoroquinolones used in the PMDT programme. Viet Nam will likely prioritize second line DST in HIV patients with rifampicin resistant TB.

Indicators of PMDT performance from 2009-2015 suggest that the increase in the screening of presumptive MDR-TB cases to detect more MDR-TB cases has affected the quality of case management. With the expansion of PMDT coverage (from 1 to 45 sites) and the increased target set for the number of cases to enroll for treatment (from 100 to 2200 patients), the conversion

and treatment success rates have decreased and are below the national set target of 75%. According to the NTP, the decrease in conversion rate from 77% to 57% -67% may be explained by lack of follow up cultures performed, and the increase in the proportion of patients still positive at month 6 (at risk of failure to treatment) which were included in denominator to calculate the indicators[17][21-23]. However, reasons for loss to follow up are unknown and patients lost to follow-up may be still infectious or even have drug resistance amplified and continue to transmit drug resistant TB to the community. The success rate achieved by Viet Nam is still overall higher compared to other LMIC countries [3]. However, the decrease in treatment success rate from 73-78% to 72-70% may be explained by the increase in those lost- to -follow up from 6-7% to 12% (both success and lost-to follow up cases were included in the denominator to calculate treatment outcome indicators)[17][21-23]. Poor links between provincial TB programs and district TB units along with unsupervised therapy while expanding PMDT may have lead to this situation[24]. Currently, the indicators used by Viet Nam are only for MDR-TB management. To monitor the detection and treatment of XDR-TB, Viet Nam should include more indicators as recently recommended by the WHO[2]. The insufficient capacity for PMDT to deal with the considerable MDR-TB cohort expansion is also reflected in the drug supply system. The stock outs during 2011-2012 were due to inadequate capacity for SLD management system to adapt the increasing number of patients [21][22].

Furthermore, regular policy changes are not communicated well to implementing sites resulting in policies not being implemented well. There is a need for the NTP to utilize standardized training modules and, possibly, distance learning tools to save resources. A clear implementation process needs to be put in place to ensure the right people receive the right information and this should be monitored and evaluated.

2.5. Conclusion

Our study reviewed WHO initiated MDR-TB policy as well as the adaptation and implementation of these policies in Viet Nam, with a special focus on case finding strategy. The study found that the policies for MDR-TB case finding in Viet Nam have been developed and revised in line with the WHO guidelines over time, with participation from key experts in the country. To address the issue of limited resources, priority was first given to people at highest risk to acquire MDR-TB, subsequently expanding to include almost all WHO recommended

targeting groups for DST. From 2012-2015, Viet Nam rapidly implemented Xpert MTB/RIF to detect TB and rifampicin resistance in MDR-TB presumptive cases.

However, inadequate communication of policy changes have led to inadequate knowledge among NTP staff on policy implementation. In addition, lack of resources posed significant challenges for the NTP to implement their policy, such as delays in management of MDR-TB contacts and in diagnosis of mono and poly resistant TB, as well as inadequate performance of second-line DST to diagnose XDR-TB .

While PMDT has been established since 2009 with policies updated following WHO's recommendations, numbers of MDR-TB cases have enrolled to treatment have remained limited compared with the estimated number of MDR-TB cases among notified TB patients. This is due to the focus of MDR-TB screening being on certain high-risk groups rather than on new TB cases. Expansion of risk groups for MDR-TB screening is key to increasing the detection of MDR-TB cases. However, in order to ensure high quality of policy implementation as PMDT is being scaled up, the NTP should standardize and decentralize training on PMDT and improve the communication about PMDT policies while sustaining and strengthening the quality of case management and treatment.

References

1. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland: WHO; 2008.WHO/HTM/TB/2008.402

2. World Health Organization . Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland: WHO; 2014, WHO/HTM/TB/2014.11.

3. World Health Organization. Global tuberculosis report 2014. Geneva, Switzerland: WHO; 2014. WHO/HTM/TB/2014.08

4. World Health Organization. Global tuberculosis report 2012. Geneva, Switzerland: WHO; 2012. WHO/HTM/TB/2012.6

5. World Health Organization. Global tuberculosis report 2013. Geneva, Switzerland: WHO; 2013. WHO/HTM/TB/2013.11

6. F. Cobelens, S. van Kampen, E. Ochodo, R. Atun, and C. Lienhardt. Research on implementation of interventions in tuberculosis control in low- and middle-income countries: a systematic review. PLoS Med., Jan. 2012. 9(12). p. e1001358.

7. The Global Fund to Fight AIDS, Tuberculosis and Malaria. Monitoring and Evaluation Toolkit, Edition 4. November. 2011.

8. National Tuberculosis Control Program of Vietnam. Mid-term development plan for TB control programme of Vietnam, 2007- 2011, Hanoi: National Tuberculosis Control Programme of Vietnam; 2006

9. National Tuberculosis Program Vietnam. Application to the GLC for access to second- line anti- tuberculosis drugs in the framework of the programmatic management of drug- resistant tuberculosis, Hanoi: National Tuberculosis Control Programme of Vietnam; 2007

10. National Tuberculosis Control Program of Vietnam. National Guidelines for Programmatic Management of Drug Resistance Tuberculosis. Hanoi: Ministry of Health; 2009: 1-142.

11. National Tuberculosis Control Program of Vietnam. Standard Operational Procedure for Programatic Management of Drug resistant Tuberculosis in Vietnam. Hanoi: Ministry of Health; 2012: 1-86

12. Thuy Thi Thanh Hoang, Nhung Viet Nguyen, Sy Ngoc Dinh, Hoa Binh Nguyen, Frank Cobelens, Guy Thwaites, Huong Thien Nguyen, Anh Thu Nguyen, Pamela Wright and Heiman F. L. Wertheim. Challenges in detection and treatment of multidrug resistant tuberculosis patients in Vietnam. BMC Public Health 2015, 15:980..

13. National Tuberculosis Control Program of Vietnam. Mid-term development plan for TB control programme of Vietnam, 2011- 2015, Hanoi: National Tuberculosis Control Programme of Vietnam; 2010: 1-125

14. Government of Viet Nam. Resolution of promoting on the Implementation of the Millenium Development Goals . 05/NQ-CP. 2014.

15. Government of Viet Nam. Decesion about approval of the National Strategy for Tuberculosis Control to 2020 and vision to 2030. 374/QĐ-TTg.

16. World Health Organization. Xpert MTB/RIF implementation manual, Technical and Operational 'How-to', Practical considerations, Geneva, Switzerland: WHO; 2014. WHO/HTM/TB/2014.1

17. National Tuberculosis Control Program of Vietnam. Annual review meeting report of the National TB Control Programme of Vietnam, 2014. Hanoi: National Tuberculosis Control Programme of Vietnam; 2014. Ref Type: Report.

18. World Health Organization. The Global Plan to stop TB, 2011-2015, Transforming the Fight towards elimination of tuberculosis. Geneva, Switzerland: WHO, 2010

19. H. T. W. Quy, N. T. N. Lan, M. W. Borgdorff, J. Grosset, P. D. Linh, L. B. Tung, D. van Soolingen, M. Raviglione, N. V Co, and J. Broekmans. Drug resistance among failure and relapse cases of tuberculosis: is the standard re-treatment regimen adequate?, Int. J. Tuberc. Lung Dis. Jul. 2003.7(7): 631–6

20. N. V Nhung, N. B. Hoa, D. N. Sy, C. M. Hennig, and A. S. Dean. The Fourth National Anti-Tuberculosis Drug Resistance Survey in Viet Nam. Int J tuber Lung dis. 2015. 19(6): 670–675.

21. National Tuberculosis Control Program of Vietnam. Annual review meeting report of the National TB Control Programme of Vietnam, 2011. Hanoi: National Tuberculosis Control Programme of Vietnam; 2011. Ref Type: Report.

22. National Tuberculosis Control Program of Vietnam. Annual review meeting report of the National TB Control Programme of Vietnam, 2012. Hanoi: National Tuberculosis Control Programme of Vietnam; 2012. Ref Type: Report

23. National Tuberculosis Control Program of Vietnam. Annual review meeting report of the National TB Control Programme of Vietnam, 2013. Hanoi: National Tuberculosis Control Programme of Vietnam; 2013. Ref Type: Report

24. B. Marais, N. Munez, C. Hennig, P. H. Khanh. Green Light Committee Monitoring Mission Report for Vietnam. The Philippines: World Health Organization -Western Pacific Regional Office; 2012: 1-88

Chapter 3. A HOUSEHOLD SURVEY ON SCREENING PRACTICES OF HOUSEHOLD CONTACTS OF SMEAR POSITIVE TUBERCULOSIS PATIENTS IN VIETNAM

Hoang Thi Thanh Thuy[1*], *corresponding authors; Email: hoangthanht@gmail.com

Dinh Ngoc Sy[1], Email: syminhquan@gmail.com

Nguyen Viet Nhung[1], Email: vietnhung@yahoo.com

Nguyen Van Hung[1], Email: hungmtb75@yahoo.co.uk

Peter Horby[2,3], Email: peter.horby@gmail.com

Frank Cobelens[4], Email: f.cobelens@amc-cpcd.org

Heiman F.L. Wertheim[2,3], Email: heiman.wertheim@gmail.com

1. National Tuberculosis Control Programme of Vietnam- National Lung Hospital (VNTP-NLH)
2. Oxford University Clinical Research Unit, Hanoi, Vietnam (OUCRU)
3. Nuffield department of clinical medicine, Centre for Tropical Medicine UK
4. Department of Global Health and Amsterdam Institute for Global Health and Development, Academic Medical Center, Amsterdam, Netherlands

Abstract

Background: Close contacts of tuberculosis (TB) patients are at increased risk of developing tuberculosis. Although passive contact screening guidelines are incorporated in the national TB control program, currently it is unknown how frequent close contacts are screened for TB in Vietnam. This study assesses current contact screening practices in Vietnam and determines the proportion of household contacts screened of newly registered TB patients.

Method: Survey of household contacts of smear-positive TB patients (index patients) registered for treatment in 2008 in three Vietnamese cities. Households were interviewed in 2010 about screening for TB since treatment registration date of the index patient.

Results: We interviewed 4,118 household contacts of 1,091 identified index cases. Contact screening mainly relied on self-referral by household contacts. Of the 4,118 household contacts, 474 (11.5%) self-referred for TB screening, while this screening proportion was only 5.5% among contacts under 5 years old (16/293). Sputum examinations were performed in 374 (78.9%) of the screened contacts. Contact screening identified 27 cases of pulmonary TB (0.7%; or 656 cases/100,000 contacts), of which 20 were detected by sputum smear.

Conclusions: The low proportion of household TB contacts screened for TB illustrates the limitations of passive contact screening as currently practiced in Vietnam. Children under 5 years of age are particularly neglected with this approach. Active contact screening with fixed follow-up times of close contacts of newly diagnosed TB patients should be considered in Vietnam, particularly in case of young children and drug-resistant TB.

Key words: Tuberculosis, contact screening, case finding, Vietnam

3.1 Introduction

The World Health Organization (WHO) reported that the detected proportion of incident global tuberculosis (TB) cases is below the WHO target of 70% [1]. One of the proposed solutions is to improve the case detection rate by active and systematic screening all household contacts of pulmonary TB patients, since they are considered to be at increased risk for TB infection [2, 3]. Although contact investigation is already a priority of tuberculosis control programs in many low burden and resource replete countries [4], in high burden and resource deplete areas contact screening for TB is often not performed due to the high workload and costs [5]. The recently issued International Standard for Tuberculosis Care states that contact investigation is an important activity and warrants more effort to ensure that persons in close contact with infectious TB patients are evaluated and managed [6].

Vietnam currently ranks 12th out of 22 countries with a high burden of TB [1]. The annual notification rate of new smear-positive pulmonary TB to the National TB Program (NTP) in recent years is about 57-58/100.000 population [7], but only accounts for 56% of new TB cases that occur annually. The remaining 44% are not diagnosed and/or diagnosed but not reported to the NTP [8]. In order to increase TB notification, the NTP utilizes both passive and active case finding strategies [9]. However in practice, due to lack of specific instructions for active case finding and insufficient resources, active case finding is rarely done. For most of the Vietnamese population, the NTP strategy relies on "passive case finding". Passive case finding needs people to self-report with TB symptoms to primary health centers, and are then screened by sputum smear. This passive case finding strategy makes use of mass media to inform the general population about TB so that they can self-refer when symptomatic. For household contacts of infectious TB patients, a similar strategy exists as for the general population. The only difference is that TB patients and their contacts get direct information and instructions from health staff regarding when the household contacts need to come for screening. We refer to this strategy as "passive contact screening".

This passive contact screening strategy is incorporated in the NTP guidelines and meets the minimum requirements for contact investigation as recommended by the WHO [10]. The requirements include: provide health education to TB patients and their household contacts, household visits and check for symptomatic contacts, perform sputum smear in case of

prolonged cough. Health education is performed either at the health facility, where patients come to take drugs, or at home when health staff visits patients. The health education includes instructions when to seek screening, with additional instructions for children <5 years such as fever for more than two weeks or failure to thrive as their symptoms may be aspecific.

There are no data on current contact screening practices in Vietnam, while these data are essential for managing the program. Therefore, we conducted a retrospective cohort study of household contacts of patients with newly diagnosed TB in three large cities in order to assess whether they follow the NTP guideline on the following aspects: (1) screening of symptomatic household contacts, (2) screening of children <5years, and (3) type of screening tests performed.

3.2 Materials and Methods

3.2.1 Study design and setting

We conducted structured interviews within the households of newly diagnosed TB patients who were registered for treatment with the NTP in 2008. The interviews were conducted between October and December 2010 in nine randomly selected districts of three large cities in Vietnam, three districts per each city: Hanoi, Ho Chi Minh City, and Da Nang. This study was approved by the research committee of the National Lung Hospital in Hanoi. Informed consent was obtained from TB patients and subsequently from their household contacts.

A standardized questionnaire was used to evaluate the contact screening practices of household contacts of TB patients. The interviews were conducted by local health staff of the TB program. The survey was done in the evening during working days and during daytime in weekends. In case of absence on 2 visits, the household was considered 'lost to follow-up'. The questionnaire sought information from the patients and their household contacts about the TB screening instructions received at the time of treatment and whether the instructions were followed. Index patients and household representatives were asked about the occurrence of prolonged cough among household contacts since the diagnosis of TB in the index case and whether these contacts went for screening or received advice from health staff regarding screening. Primary caregivers provided the answers concerning children.

3.2.2 Study population and definitions

The study population consisted of smear-positive TB patients registered for treatment in 2008 in one of the 9 districts mentioned above (index patients), satisfying at least one of the following criteria: (1) >1 smear- positive samples (from two different sputum specimens), or (2) one smear-positive sample and an abnormal chest Xray (CXR) consistent with TB, or (3) a positive culture with or without positive smear. For the survey we included household contacts of notified TB cases. The following definitions were used:

- Household contact: an individual that shared the same house with the index case for a period of at least 3 months leading up to the time of diagnosis of the index case.

- Screened household contacts: a household contact who attended a public or private health facility for TB screening in the interval (days) between the day treatment was started of the index case and the interview date of the household.

- Secondary case: a household contact who was diagnosed to have TB in the interval (days) between the day start of treatment of the index case and the day of interview of the household.

- Prolonged cough: unexplained cough of more than two weeks duration occurring between the start of treatment of the index case and the interview of the household.

3.2.3 Data collection and analysis

The data were collected through the NTP district coordinators. The staff of commune health stations conducted the household interviews after study specific training was provided. Data were entered into Microsoft Access software, and exported to SPSS (version 17.0) for analysis. Data quality was monitored by cross-checking 10% of the data entered in to the database against the original paper-based questionnaire. Descriptive statistics, including frequency, median, interquartile range (IQR), proportion and 95% confidence intervals (95% CIs), were performed where appropriate. Proportions were compared using the chi-squared test. P–values below 0.05 were considered significant (two-sided).

3.3 Results

3.3.1 Demographic and clinical characteristics of study population

We interviewed the household contacts of 1,091/1,215 (89.8%) smear-positive TB patients registered in 2008 in the nine selected districts. Households of 124 index TB patients (10.2%) did not participate in the study because of the death of the index case, absence at the time of interview, or having moved to another address.

Demographic and clinical characteristics of index TB patients and their household contacts are described in Table 3-1. The male-to-female ratio was approximately 3:1. Of the 1091 index patients, 90 (8.2%) were HIV positive and 77 (7.1%) had a history of drug abuse. Of 4118 household contacts, 293 (7.1%) were children under 5 years of age at the time of the interview, and 142 had prolonged productive cough at any time between registration of index patient and the interview (3.4%; 95% CI 2.9-4.0%; Figure 3-1). Of 1,091 index patients, 1,017 (93.2%) stated that none of their family members, other than the index case, had ever had a diagnosis of TB.

Table 3-1. Characteristics of study population

Category	Characteristics		n	%
Index TB patients				
	Sex	Male	816	74.8
		Female	275	25.2
	Age	<5	0	0.0
		5- 14	0	0.0
		15-24	136	12.5
		25-34	178	16.3
		35-44	234	21.4
		45-54	231	21.2
		55-64	139	12.7
		>=65	173	15.9
Household contacts				
	Age	<5	293	7.1
		5- 14	631	15.3
		>15	3194	77.6
Household contacts who went for TB screening				
	Sex	Male	170	35.9
		Female	304	64.1
	Age	<5	16	3.4
		5- 14	31	6.5
		>15	427	90.1
Household contacts with smear examination				
	Sex	Male	132	35.3
		Female	242	64.7
	Age	<5	2	0.5
		5- 14	13	3.5
		>15	359	96.0
Secondary TB cases detected from contacts (any test)				
	Sex	Male	13	48.1
		Female	14	51.9
	Age	<5	1	3.7
		5- 14	2	7.4
		>15	24	88.9
Secondary TB cases detected from contacts (positive smear)				
	Sex	Male	11	55.0
		Female	9	45.0
	Age	<5	0	0.0
		5- 14	2	10.0
		>15	18	90.0

*TB = tuberculosis

Figure 3-1. Flow chart of tests taken for household contacts of smear-positive TB patients in three cities of Vietnam, 2008-2010.

Household contacts of TB patients
n=4118

Prolonged cough
n=142

Cough unknown or no cough
n=3976

Not screened
n=39

Screened
n=103

Screened
n=371

Not screened
n=3605

No diagnostics done
n=4

Xray done
n=11

Sputum smear
n=88

Sputum smear
n=286

Xray done
n=65

Missing data
n=13

No diagnostics done
n=7

Abnormal consistent with TB, n=4

Positive smear
n=17

Positive smear
n=3

Abnormal consistent with TB
n=3

Positive smear
n=20

3.3.2 Household screening

The median number of household contacts per index patient was 3.8 (IQR: 3 - 5). During the interval between the registration of the index case and the interview, at least one household

contact was screened for 335/1,091 (30.7%; 95% CI: 28.0-33.4%) index patients. A total of 474/4,118 (11.5%; 95% CI: 10.5-12.5%) of all household contacts sought TB screening, including 16/293 (5.5%; 95% CI: 2.9-8.1%) contacts aged under 5 years (Figure 3-2). The rate of screening was higher (p-value <0.05) among those with prolonged cough (103/142; 72.5%; 95% CI: 65.2-79.9%) than among those without prolonged cough and/or cough unknown (371/3976; 9.3%; 95% CI: 8.4-10.2 % Figure 3-1). Detailed information regarding the examinations performed was available for 461/474 (97%) individuals who went for TB screening. Smear examination was done for 374/461 contacts (81.1%), 76 (16.5%) contacts only had CXR and 11 (2.4%) had neither sputum nor CXR examination (Figure 3-1). Of 103 contacts with prolonged productive cough who were screened, 88 were tested by direct sputum smear examination (85.4%; 95% CI: 78.6-92.3%), 11 (10.7%; 95% CI: 4.7-16.6%) only by CXR and 4 (3.9%; 95% CI: 0.2-7.6%) had no specific TB testing. There was no significant difference in the proportion of contacts that went for TB screening by smear grade of the index case (p value =0.23, Table 3-2).

Figure 3-2. Venn diagram for screening of household contacts of smear-positive TB patient in three cities of Vietnam, 2008–2010.

Contacts had sputum exam[c]

All ages (< 5 ys): n=374 (2)

Household contacts[a]:

All ages (< 5 ys): n=4118 (293)

Contacts went for TB screening[b]:

All ages (< 5 ys): n=474 (16)

TB case detected[d]

All ages (< 5 ys): n=27 (1)

96
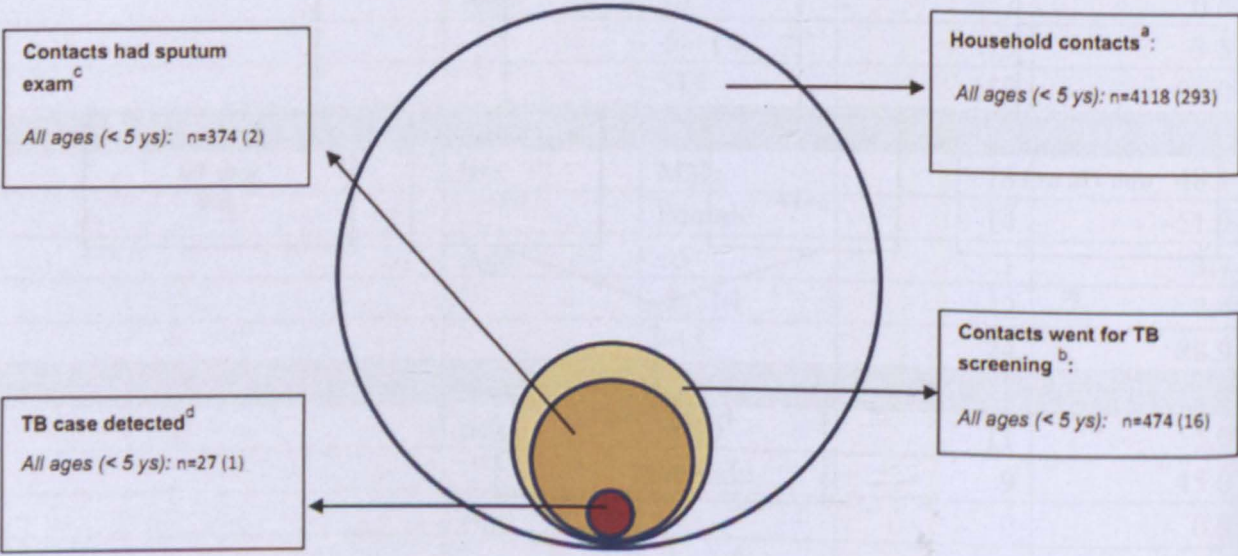
Table 3-2. Screening for contacts grouped by sputum grade of index patients

Positivity grade of index cases[a]	No of Index patient	No of contacts	Contacts per index case	Contacts went for screening n(%)		Secondary cases with positive smear; n(%)	
3+	144	563	3.9	75	(13.3)	3	4.0%
2+	183	699	3.8	75	(10.7)	3	4.0%
1+	610	2249	3.7	265	(11.8)	9	3.4%
Scanty	154	607	3.9	59	(9.7)	5	8.5%
Total	1091	4118	3.8	474	11.5%	20	4.2%

[a]*Based on the International Union Against Tuberculosis and Lung Disease (IUATLD)-recommended grading of sputum smear microscopy results*

Just 103 (21.7%) symptomatic contacts that went for screening had prolonged productive cough, and the remaining 371 (78.3%) had no prolonged cough and/or cough unknown. 39 contacts with prolonged cough did not go for screening. Reported reasons for not going for screening included: busy earning a living, feeling better after self-medication with over-the-counter drugs, and afraid of unaffordable treatment cost.

Among the 4,118 household contacts, 27 secondary TB cases were detected (detection rate: 0.7% or 656 patients/100,000 contacts), of which 13 were male. One TB case was detected among children under 5 years of age (Table 3-3). 20 contacts with TB were diagnosed by positive sputum smear and 7 by CXR (Figure 3-1). There is a significant difference in proportion of TB detected between contacts with prolonged cough vs without prolonged cough or unknown (p<0.001, table 3.3).

Table 3-3. TB case detected among contacts of smear positive TB patients

Contact by characteristic		Contacts went for screening*	Contacts with sputum examination	Total TB cases detected **	Smear positive TB cases detected	
Types	*number*					
All household contact	4118	474	374	27	20	
Contacts with prolonged cough	142	103	88	21	17	*P<0.001*
Contacts without prolonged cough or cough unknown	3976	371	286	6	3	
Children under 5 years of age	293	16	2	1	0	

Includes contacts who came to public or private health facility for screening

**Either with smear- positive or smear-negative tuberculosis detected from contacts*

TB=tuberculosis

The index patients had a median duration of 2 days (IQR: 1-4 days) from diagnosis to treatment. The median duration from treatment registration of the index case to screening of contacts was 29 days (IQR: 9-65 days), and for TB positive contacts this was 97 days (IQR: 37-316 days).

Most index patients (n=722; 66.2%) were aware that any adult contact with prolonged cough should go for TB screening. Sixty-nine (6.3%) index patients thought screening was not required for household contacts and only 68 (6.2%) were aware of the risks for children under 5 years of age in their household.

3.4 Discussion

This study shows that with the current system of passive contact screening for TB, ~10% of all household contacts are screened, and just 5.5% of children under 5 years of age. These rates are

low and need to be improved as studies show that up to 22% of household contacts in high prevalence countries have TB [5]. The low proportion of household contacts screened is likely a consequence of the passive nature of the strategy, which mainly relies on typical clinical symptoms being experienced by the contact and persons seeking appropriate health care on their own initiative [11]. In this study, several contacts did not go for TB screening even when they experienced prolonged cough. Reported reasons for this are related to unawareness about the need for screening and fear of costly diagnosis and treatment. Although the vast majority of TB patients (66%) knew about the need for investigating contacts, one-third were not aware that contacts with prolonged cough need to be screened. Furthermore, very few of the TB patients (6.2%) knew that young children need to be screened in case of suspect symptoms, and as a result children under 5 years of age are usually ignored. There is a need to evaluate the effectiveness of health education materials and methods being used in the NTP to optimally utilize them so that contact tracing can be performed more effectively.

Currently the NTP only focuses on contacts that self-report to a health facility with a persistent productive cough for at least 2 weeks [9, 12]. A large TB prevalence survey in 2006-2007 in Vietnam revealed that 47% of TB cases had other symptoms than cough or only chest X ray abnormalities [8]. Thus half of the patients may be missed if the program only focuses on cough. Another issue that may contribute to under-diagnosis is the method of screening for TB. According to the Vietnam NTP guidelines, direct smear examination is the main diagnostic test provided for people who present themselves at a health facility with symptoms suggestive of TB. However, in this study, 15% of TB contacts with a prolonged productive cough who went for screening were not examined by sputum smear.

In order to improve TB case detection, systematic contact investigations need to be considered for implementation in low income and middle income countries with endemic TB levels [13]. The potential yield of TB cases from contact investigation in high- and low-incidence settings has been reviewed previously [4, 5]. In a meta-analysis, the prevalence of TB among all household contacts is estimated to be 3.1% [4]. In high-prevalence countries, up to 22% of household contacts have active tuberculosis [5]. Furthermore, in settings with high proportion of HIV-positive TB cases, active screening among household contacts yields nine times more TB cases as compared to passive case finding [14]. Recently, programs are starting to utilize

resources for targeted screening of contacts of MDR-TB patients, HIV positive contacts and children [15].

This study has several limitations. We collected data over a limited time period (from index patients registered for treatment in 2008 up to the time of the interview in October to December 2010. Also the retrospective nature of this study may result in recall bias. We may have therefore missed TB disease among contacts that either developed disease after our study or may nor recall correctly. As the questions were simple and straightforward on a major health issue in the household, we believe we were able to minimize recall bias. Furthermore, several studies have shown that the highest proportion of TB cases among contacts are detected in the first two years after exposure and therefore we think only few may have developed disease after our study [4, 16].

Furthermore, it is difficult to conclude whether the detected TB cases among contacts went for screening due to the health education provided to them at the time of the index case diagnosis or due to other reasons. However, as most TB cases among contacts were diagnosed relatively shortly after the diagnosis and treatment of the index case (~3 months) we believe that the majority went for screening as a result of instructions provided to them at the health education. Another limitation is that no rural areas were included in this study and our findings only apply to urban areas. There may be better screening practices in urban areas due to higher education levels and knowledge about TB, better access to health facilities and more resources for TB diagnostics.

Another limitation was that the assessment of NTP guidelines regarding contact screening was done by health staff, who are also part of implementing these NTP guidelines (i.e. TB unit staff). This may have biased the results. However, the interviewers were trained in survey techniques and were instructed not to be concerned about 'right' or 'wrong' answers. Furthermore, the study progress was supervised by two independent supervisors (FC and HW). Since the results are not supportive of the current program, we believe we have been successful in minimizing bias.

3.5 Conclusions
This study shows that the proportion of household contacts of smear-positive tuberculosis patients screened for TB under the current passive screening approach of the Vietnam National

TB program is very low compared with prevalence of TB among contacts in high burden countries. Better health information and instructions need to be provided to contacts of TB patients to improve their health seeking behavior in case of possible TB symptoms, with a focus on vulnerable groups like HIV-positive contacts, contacts of drug resistant TB cases and contacts under 5 years of age. Special attention is needed to provide guidance when to seek TB screening for children. Contact investigation should be conducted more actively and systematically starting by recording the contacts information for management and follow-up. Active contact tracing of close contacts of newly diagnosed TB patients should be considered in Vietnam, particularly in case of young children and drug-resistant TB. Studies that assess how this can be efficiently done are required.

Reference

1. World Health Organization. Global Tuberculosis Report 2013, World Health Organization Document 2013. 2013:1-289. WHO/HTM/TB/2013.11

2. World Health Organization. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countrie, World Health Organization Document 2012. 2012:1-65. WHO/HTM/TB/2012.9

3. Veen J. Microepidemics of tuberculosis: the stone-in-the-pond principle. Tuber Lung Dis 1992;73:73-6.

4. Fox GJ, Barry SE, Britton WJ, Marks GB:Contact investigation for tuberculosis. a systematic review and meta-analysis. The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology 2012; 1-46:doi:10.1183/09031936.00070812

5. Rieder H L. Contacts of tuberculosis patients in high-incidence countries. Int J Tuberc Lung Dis 2003;7(suppl 3):S333-S336

6. Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care, Edition 3. TB CARE I, The Hague, 2014.

7. National Tuberculosis Control Program of Vietnam. Annual data collection from National TB control Programme of Vietnam. Hanoi: National Tuberculosis Control Program; 2008-2013; Ref Type: Report

8. Hoa N B, Sy D N, Nhung N V, Tiermersma E W, Borgdorff M W, Cobelens F G J. National survey of tuberculosis prevalence in Viet Nam. Bull World Health Organ 2010;88:273-80

9. National Tuberculosis Control Program of Vietnam. National Guidelines for TB control Programme of Vietnam; 1-169. Hanoi: Ministry of Health; 2009.

10. World Health Organization. Implementing the WHO Stop TB Strategy. A handbook for national tuberculosis control programmes. World Health Organization Document 2008;WHO/HTM/TB/2008.401:1-184

11. World Health Organization. Scoping meeting for the development of guidelines on screening for active TB. Geneva, Switzerland: World Health Organization, Draft meeting report; 2011

12. Huong N T, Duong B D, Co N V, Quy H T, Tung L B, Bosman M, et al. Establishment and development of the National Tuberculosis Control Programme in Vietnam. Int J Tuberc Lung Dis 2005;9:151-6

13. Morrison J, Pai M, Hopewell PC. Tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis.Lancet Infect Dis. 2008;8:359–68.

14. Zachariah R, Spielmann M P, Harries A D, Gomani P, Graham S M, Bakali E, et al. Passive versus active tuberculosis case finding and isoniazid preventive therapy among household contacts in a rural district of Malawi. Int J Tuberc Lung Dis 2003;7:1033-9

15. Fox GJ, Dobler CC,Marks GB. Active case finding in contacts of people with tuberculosis (Review).TheCochraneLibrary2011.http://www.thecochranelibrary.com.

16. Fox GJ, Nhung N V, Sy D N, Britton WJ , Marks GB. Cluster Randomized Controlled Trial Of Household Contact Investigation In 8 Provinces In Vietnam. ATS Journals 2013.

Chapter 4. CHALLENGES IN DETECTION AND TREATMENT OF MULTIDRUG RESISTANT TUBERCULOSIS PATIENTS IN VIETNAM

Hoang Thi Thanh Thuy[1*], *corresponding author; Email: hoangthanht@gmail.com

Nguyen Viet Nhung[1], Email: vietnhung@yahoo.com

Dinh Ngoc Sy[2], Email: syminhquan@gmail.com

Nguyen Binh Hoa[1,3], Email:nguyenbinhhoatb@yahoo.com

Frank Cobelens[4], Email: f.cobelens@amc-cpcd.org

Guy Thwaites[5,6] Email: gthwaites@oucru.org

Nguyen Thien Huong[7]: nthuong139@gmail.com

Nguyen Thu Anh[8], Email: thuanh.nguyen@sydney.edu.au

Pamela Wright[9], Email:pamela.wright@mcnv.nl

Heiman F.L. Wertheim[6,10,11] Email: heiman.wertheim@gmail.com

1. National Tuberculosis Control Program of Vietnam- National Lung Hospital (VNTP-NLH)
2. Vietnam Association for Tuberculosis and Lung Disease, Hanoi, Vietnam
3. Centre for Operational Research, International Union Against Tuberculosis and Lung Disease, Paris, France
4. Department of Global Health and Amsterdam Institute for Global Health and Development, Academic Medical Center, Amsterdam, Netherlands
5. Wellcome Trust Major Overseas Program, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam
6. Nuffield Department of Clinical Medicine, Centre for Tropical Medicine, University of Oxford, United Kingdom.
7. KNCV Tuberculosis Foundation, Vietnam Country Office, Hanoi, Vietnam
8. Woolcock Institute Of Medical Research, Australia
9. Medisch Comite Nederland-Vietnam, Netherlands
10. Wellcome Trust Major Overseas Program, Oxford University Clinical Research Unit, Hanoi, Vietnam (OUCRU)
11. Department of Medical Microbiology, Radboudumc, Nijmegen, Netherlands

Abstract

Background: Vietnam is ranked 14th among 27 countries with high burden of multidrug-resistant tuberculosis (MDR-TB). In 2009, the Vietnamese government issued a policy on MDR-TB called Programmatic Management of Drug-resistant Tuberculosis (PMDT) to enhance and scale up diagnosis and treatment services for MDR-TB. Here we assess the PMDT performance in 2013 to determine the challenges to the successful identification and enrollment for treatment of MDR-TB in Vietnam.

Methods: In 35 provinces implementing PMDT, we quantified the number of MDR-TB presumptive patients tested for MDR-TB by Xpert MTB/RIF and the number of MDR-TB patients started on second-line treatment. In addition, existing reports and documents related to MDR-TB policies and guidelines in Vietnam were reviewed, supplemented with focus group discussions and in-depth interviews with MDR-TB key staff members.

Results: 5,668 (31.2%) of estimated 18,165 MDR-TB presumptive cases were tested by Xpert MTB/RIF and second-line treatment was provided to 948 out of 5,100 (18.7%) of MDR-TB patients. Those tested for MDR-TB were 340/3,224 (10.5%) of TB-HIV co-infected patients and 290/2,214 (13.1%) of patients who remained sputum smear-positive after 2 and 3 months of category I TB regimen. Qualitative findings revealed the following challenges to detection and enrollment of MDR-TB in Vietnam: insufficient TB screening capacity at district hospitals where TB units were not available and poor communication and implementation of policy changes. Instructions for policy changes were not always received, and training was inconsistent between training courses. The private sector did not adequately report MDR-TB cases to the NTP.

Conclusions: The proportion of MDR-TB patients diagnosed and enrolled for second-line treatment is less than 20% of the estimated total. The low enrollment is largely due to the fact that many patients at risk are missed for MDR-TB screening. In order to detect more MDR-TB cases, Vietnam should intensify case finding of MDR-TB by a comprehensive strategy to screen for MDR-TB among new cases rather than targeting previously treated cases, in particular those with HIV co-infection and contacts of MDR-TB patients, and should engage the private sector in PMDT.

Key words: Multi drug resistant tuberculosis, detection, treatment, Vietnam

4.1 Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a global health concern as treatment is prolonged, costly, and less effective compared to that of drug-susceptible TB. Globally, there are about 450,000 MDR-TB patients reported with an estimated 170,000 MDR-TB-related deaths annually. Regarding the TB and MDR-TB epidemiology in Vietnam, the country is ranked 12 nd among 22 high burden countries with TB, and 14th among 27 countries with a high burden of MDR-TB. The incidence of TB in Vietnam is estimated at 144 per 100,000 population per year and the estimated prevalence is 209 cases per 100,000 population [7]. There are estimated to be about 5100 MDR-TB cases among notified TB cases per year. The proportion of TB cases with MDR-TB among new and retreatment cases is estimated to be 4 and 23 %, respectively, with around 6 % among TB cases co-infected with HIV [7]. A preliminary report from a TB drug resistance survey conducted in Vietnam from 2011–2012 showed that the estimated proportion of XDR-TB among MDR-TB was 5.6 %. Of the MDR-TB patients, 16.7 % showed resistance to fluoroquinolones (ofloxacin), 1.1 % to amikacin, 5.6 % to kanamycin, and 5.6 % to capreomycin (unpublished data).

In 2009, the Vietnamese government issued a policy on MDR-TB following. WHO recommendations to enhance and scale up diagnosis and treatment services for MDR-TB [11]. It is based on the five essential control components that constitute the already implemented DOTS strategy for drug-susceptible TB. These components include: sustained political commitment, rational case finding, short-course treatment, an uninterrupted drugs supply, and standardized recording and reporting [8]. Since a pilot project in Ho Chi Minh City in 2009, diagnosis and treatment services for MDR-TB have become available in 35 of all 63 provinces by 2013. The programmatic management of drug-resistant tuberculosis (PMDT) is more complex than for susceptible TB as it requires greater human, financial and technical resources [8]. Between 2009 and 2011 the Vietnam PMDT program had a success rate, defined as MDR-TB patients who completed treatment and were cured, of approximately 75 %. This rate is high compared to many other countries reporting rates of 44–58 % [5][6]. Despite that the treatment outcome may depend on drug resistance patterns, this high success rate does reflect good compliance with the treatment regimen in Vietnam [10]. The current standard second-line regimen is kanamycin, capreomycin, levofloxacin, cycloserine, protionamide, and para-aminosalicyclic acid (PAS).

However, the number of MDR-TB patients detected and enrolled to second-line treatment is low compared to the expected number among notified TB cases, based on national drug susceptibility data [4]. This means that only a few of the MDR-TB patients get diagnosis and the recommended treatment. This can partly be explained by the fact that Vietnam did not have nation-wide PMDT coverage by 2013, and drug susceptibility testing was not yet done for all notified TB cases. However, PMDT was fully implemented in major cities by 2010, where just 30–50 % of the total estimated MDR-TB patients were enrolled for second-line treatment. This finding lead us to assess the proportion of MDR-TB patients enrolled out of the estimated number of MDR-TB in all PMDT areas of Vietnam in 2013 to determine the challenges to an efficient PMDT implementation and to provide recommendation to improve the PMDT enrollment.

PMDT includes five steps from diagnosis to treatment for MDR-TB patients:(1) identification of presumptive MDR-TB cases (individuals considered at high risk for MDR- TB) according to case definitions, (2) referring presumptive cases for diagnosis, (3)drug resistance testing, (4) obtaining informed consent from patients for treatment, and (5) enrollment of diagnosed MDR-TB patients to treatment. In this assessment, we used the data reported by the national TB control program to focus on three of these steps: identification of presumptive MDR-TB cases, drug resistance testing, and enrollment of diagnosed MDR-TB patients for treatment. Qualitative investigation was used for assessment of steps (2) and (4) and additionally to support the findings and their interpretation for the other steps.

4.2 Materials and Methods

By 2013, 35 provinces had implemented the PMDT and participated in the MDR-TB enrollment assessment. Thirty-one provinces were selected by the NTP to implement PMDT based on their prior MDR-TB case-load and case management capacity. The remaining four provinces with a low MDR-TB case-load were selected as they had a high HIV prevalence. All 35 provinces were provided access to diagnostic equipment for intensified case finding using the Xpert MTB/RIF (Xpert) assay, a within-cartridge real-time PCR assay that detects M. tuberculosis as well as mutations in the rpoB gene conferring resistance to rifampicin in clinical specimens [15]. The selected provinces are required to provide PMDT treatment services in case MDR-TB patients

are diagnosed. For the assessment, we reviewed all existing reports and documents related to MDR-TB policies and guidance since 2009 through December 2013.

A presumptive MDR-TB case requiring testing was defined as belonging to at least one of the risk groups as defined in the NTP guidelines (see Appendix 1). In order to calculate the proportion of those screened for MDR-TB, we divided the number of tested presumptive MDR-TB cases by the number of presumptive MDR-TB cases estimated using annual data reported by each province to the NTP (step1). All PMDT provinces provide quarterly reports to the NTP of the number of Xpert MTB/RIF tests done and the number of MDR-TB cases detected. We used the 2013 Xpert MTB/RIF data for assessing the number of presumptive cases screened per risk category (step 3).

For national estimation of MDR-TB, we used the number of all notified TB cases per province and applied the result of the most recent national DRS in Vietnam (year 2011–2012). Eligible cases to be enrolled in the DRS were smear-positive TB patients (both new and previously treated TB patients) registered for treatment in the selected clusters during the period of recruitment (between June and December 2011). The DRS showed prevalence of MDR-TB among new and previously treated cases of 4.0 % and 23.0 %, respectively [7]. This allowed us to estimate the expected number of incident MDR-TB cases in all provinces irrespective of detection by the NTP. We used the standard errors from the MDR-TB prevalence as estimated in the DRS to calculate confidence intervals for the proportion of MDR-TB patients enrolled for second-line treatment in this study. The proportion with 95 % confidence intervals (95 % CI) was estimated for the number of MDR-TB patients enrolled for second-line treatment among (i) the estimated number of MDR-TB cases in the whole country and (ii) the estimated number of MDR-TB cases in the 35 PMDT provinces (step 5).

This review was followed by focus group discussions (FGD) in face-to-face workshops, which encompassed five separate one-day sessions with approximately 30 key provincial TB staff members (for all PMDT steps including steps 2 and 4). FGD were used to discuss the PMDT program, challenges to implementation and potential solutions. Five groups were invited from eight different geographic areas (see Appendix 1). TB staff included provincial program managers, program officers with expected knowledge of the local overall situation and staff responsible for implementation of PMDT in their province. Guidance was provided for FGD

facilitators who had previous FGD discussion experience and knowledge of the NTP. Discussions were continued until saturation was reached before facilitators moved to a new topic. FGD summaries were checked and agreed upon by all participants to be finalized for content analysis later on. The sessions were not audio recorded and transcribed due to lack of funds.

Furthermore, in-depth interviews to supplement the focus group discussions was conducted by the same group of interviewers with eighty TB health staff at different levels of the NTP, including 8 central staff from PMDT team, 56 provincial staff from variety of departments, and 16 district and commune level health staff (for all steps). The interview guide was developed and piloted before the interviews and included questions regarding: structure of the TB health unit at specific levels in the health system, training provided to staff, their knowledge and awareness about MDR-TB risk groups, their role and job description, and challenges encountered in PMDT implementation. The in-depth interview also allowed the interviewee to reflect on findings from the FGD. These interviews were conducted during monitoring visits in 2014 in eight randomly selected provinces among the 35 PMDT provinces from three zones: four provinces were randomly selected from the southern zone as there exists the highest disease burden, two from the north and two from the centre (see Appendix 1). The interviews were conducted privately. During the interview and FGDs, detailed notes were taken and used subsequently to identify key themes. In the analysis, similarities and differences between the various interviews and FGDs were looked for and summarized to identify key findings. The interviews were not recorded.

This study was approved by the research and ethics committee of the National Lung Hospital in Hanoi. Informed consent was obtained from participants in workshops and in-depth interviews.

4.3 Results

4.3.1 The estimated number of MDR-TB cases in Viet Nam

Based on the notification report of the NTP in 2013 and the results of the recent national DRS, we estimated that in 2013 there were 5065 (95 % CI: 3355–6700) MDR-TB patients among 102,196 notified TB cases, resulting in a proportion of 5.0 % MDR-TB among notified cases for the year 2013 (95 % CI: 3.3–6.6 %). These cases were mainly concentrated in the South–East, Mekong Delta and Red River Delta regions. The PMDT program already covered provinces with

an expected high number of MDR-TB cases (Figure4-1 and Table 4-1). We estimated that the majority 3982/5065 (78.6 %) of the national MDR-TB case-load originates in the provinces participating in the PMDT (Table 4-1).

Figure 4-1. Estimated number of MDR-TB patients among notified TB cases in Viet Nam, 2013

Estimated number of MDR-TB

- 0 - 28
- 29 - 66
- 67 - 109
- 110 - 221
- 222 - 939

PMDT
(Provinces with Programmatic Management of Drug-resistant Tuberculosis)

Paracel Islands

Spratly Islands
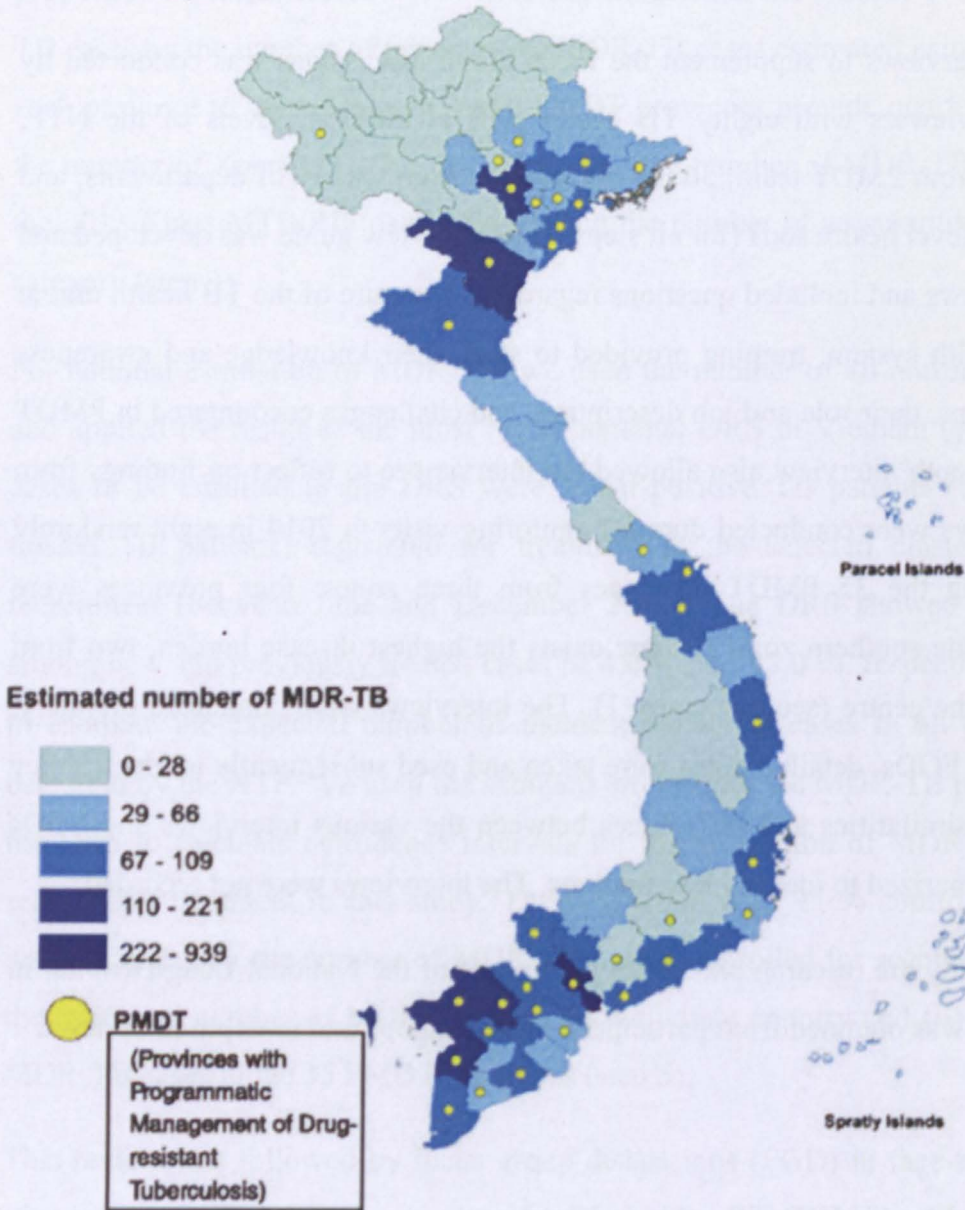
Table 4-1. Actual enrollment and estimated total number of MDR-TB cases nationwide and in 35 PMDT provinces (the numbers in brackets are for lower and upper CI)

Ser.No	Region	Number enrolled	All provinces		35 PMDT provinces		% estimated number of MDR-TB covered PMDT provinces
			Estimated number of MDR-TB cases	% enrolled	Estimated number of MDR-TB cases	% enrolled	
1	Red River Delta	234	859 (565–1,139)	27.3 (20.5–41.4)	627 (414–830)	37.3 (28.2–56.5)	73.0 %
2	North-East	0	339 (223–449)	0.0	189 (124–252)	0.0	56.0 %
3	North-West	0	53 (35–71)	0.0	9 (6–12)	0.0	17.0 %
4	Northern Central	54	466 (305–618)	11.6 (8.7–17.7)	338 (222–449)	16.0 (12.0–24.3)	72.7 %
5	Southern Central Coast	84	405 (266–536)	20.8 (15.7–31.5)	304 (200–403)	27.6 (20.8–41.9)	75.2 %
6	Central Highland	0	110 (72–146)	0.0	21 (14–27)	0.0	18.8 %
7	South –East	495	1,546 (1,035–2,036)	32.0 (24.3–47.8)	1,408 (944–1,854)	35.2 (26.7–52.4)	91.1 %
8	Mekong Delta	81	1,288 (854–1,704)	6.3 (4.8–9.5)	1,086 (720–1,436)	7.5 (5.6–11.3)	84.3 %
	Total	948	5,065 (3,355–6,700)	18.7 (14.1–28.3)	3,982 (2,643–5,264)	23.8 (18.0–35.9)	78.6 %

4.3.2 Identification of MDR-TB presumptive cases to be tested (step 1)

In 2013, there were an estimated 18,165 cases identified as presumptive MDR-TB nationally, with the majority (n = 14,998) in the 35 PMDT provinces (82.6 %). There was no data available on the number of MDR-TB presumptive cases identified by the health staff of PMDT areas who were referred for screening.

4.3.3 Testing practices per risk category by Xpert MTB/RIF and detection of MDR-TB (step 3)

A total of 32 Xpert MTB/RIF instruments were distributed among the 35 PMDT provinces. The estimated number of MDR-TB cases to be detected per machine per year for these instruments

varied by region, ranging from 9 to 338 MDR-TB cases (see Appendix 1). The instrument's capacity is expected to be sufficient as one instrument with four modules is able to test approximately 3000 MDR-TB presumptive cases to detect around 500 rifampicin resistant TB cases per year (see Appendix 1).

The proportion of MDR-TB presumptive cases tested by Xpert MTB/RIF was 31.2 % (5668/18,165) for the whole country and 37.8 % (5668/14,998) in the 35 PMDT provinces (Table 4-2). In PMDT provinces, the highest proportion of MDR-TB presumptive cases tested was in the North-West (43/46; 93.9 %) and the Southern Central Coast (668/897; 74.5 %) regions. The lowest proportions were in the Central Highlands (0/69; 0 %) and the Mekong Delta (516/3935; 13.1 %; Table 4-2) regions. In the North-West region, all provinces together only had 43/214 (20.1 %) of presumptive cases tested while that percentage was 43/46 (93.9 %) in the PMDT provinces. Among 5668 MDR-TB presumptive cases tested, 997 cases were detected as rifampicin resistant (17.6 %).

Table 4-2. Percentage of presumptive MDR-TB patients tested by regions

Ser.No	Region	Number of presumptive MDR-TB patients tested	All provinces		35 PMDT provinces	
			Estimated number of presumptive MDR-TB patients	% tested	Estimated number of presumptive MDR-TB patients	% tested
1	Red River Delta	801	2,519	31.8 %	2,035	39.4 %
2	North-East	263	1,154	22.8 %	627	42.0 %
3	North-West	43	214	20.1 %	46 [a]	93.9 %
4	Northern Central	460	1,144	40.2 %	886	51.9 %
5	Southern Central Coast	668	1,117	59.8 %	897	74.5 %
6	Central Highland	0	290	0.0 %	69	0.0 %
7	South –East	2,917	6,991	41.7 %	6,503	44.9 %
8	Mekong Delta	516	4,736	10.9 %	3,935	13.1 %
	Total	5,668	18,165	31.2 %	14,998	37.8 %

[a] *one PMDT province in North – West*

The proportions of HIV infected TB cases and new TB non-converters tested by Xpert MTB/RIF were 10.5 % (340/3224) and 13.1 % (290/2214), respectively (Table 4-3). Retreatment patients who showed no sputum conversion after 3 months of the category II regimen were tested frequently: 85.7 % (413/482). We estimated that 249/402 (62.0 %) of symptomatic household contacts of MDR-TB patients were tested. Among 249 MDR-TB symptomatic household contacts screened within 1 year after MDR-TB patients diagnosed, 77 TB patients were detected (30.9 %) including 9 TB patients resistant to rifampicin (3.6 %). We could not calculate the testing rate among failure cases since no data were available for the number of people tested. However, this rate was estimated to be at least 68.5 % because one failure case could receive up to two tests.

Table 4-3. Presumptive MDR-TB patients estimated and tested by risk category in the whole country and in 35 PMDT provinces of Vietnam 2013

Presumptive category		Estimate number for whole country [a]	Estimate number for PMDT areas only	Number of Xpert tests performed	% tested in PMDT areas
Retreatment	Failure [b]	593	519	711	ND
	Relapse	7,059	5,673	2,641	46.6 %
	Defaulters	472	376	129	34.3 %
	Other	739	662	210	31.7 %
Non-converters at 2 and 3 months	New	2,713	2,214	290	13.1 %
	Retreatment	586	482	413	85.7 %
MDR contacts		402	402	249	62.0 %
TB/HIV		3,828	3,224	340	10.5 %
>1 month using TB drugs		1,773	1,446	685	47.4 %
Total MDR-TB suspects		18,165	14,998	5,668	37.8 %

[a] The denominator is the number of presumptive by categories that need to be tested

[b] Failure is defined as sputum smear positive at 5 months or later during treatment, so one failure case could receive one or 2 tests (at 5 and/or 7 months). ND: not done as failure cases can be tested on multiple occasions

4.3.4 Enrollment to second-line treatment (step 5)

Of 997 rifampicin-resistant cases detected, 948 (95.1 %) were enrolled for MDR-TB treatment, accounting for just 18.7 % (95 % CI: 14.1–28.3 %) of the estimated 5065 MDR-TB cases in the whole of Vietnam (Figure4-2). The region with the highest proportion of MDR-TB patient enrolled for second-line treatment was the South-East region with 495/1546 (32.0 %; 95 % CI: 24.3–47.8 %), followed by the Red River Delta with 234/859 (27.3 %; 95 % CI: 20.5–41.4 %). The lowest enrollments were in the Mekong Delta region: 81/1288 (6.3 %; 95 % CI: 4.8–9.5 %). No enrollments were reported in PMDT for North-East, North-West and Central Highlands (Table 4-1, Figure4-3). Also in the 35 PMDT provinces, the enrollment proportion of MDR-TB cases was low: 948/3982 (23.8 %; 95 % CI:18.0–35.9 %). The highest proportion was seen in the PMDT provinces in the Red River Delta with 234/627(37.3 %; 95 % CI: 28.2–56.5 %), and South-East region: 495/1408 (35.2 %; 95 % CI: 26.7–52.4 %)

Figure 4-2. PMDT performance for case detection and enrollment of MDR-TB in Vietnam

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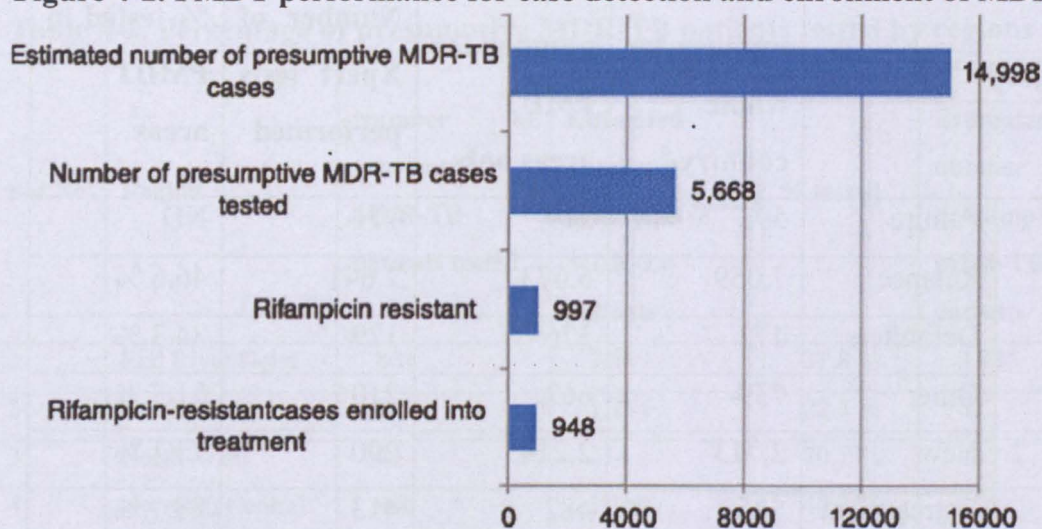
Figure 4-3. The enrollment proportion into the second-line treatment program of MDR-TB cases among the estimated number of notifiable MDR-TB cases in 35 PMDT provinces in 2013. Data are presented per socio-economic region.
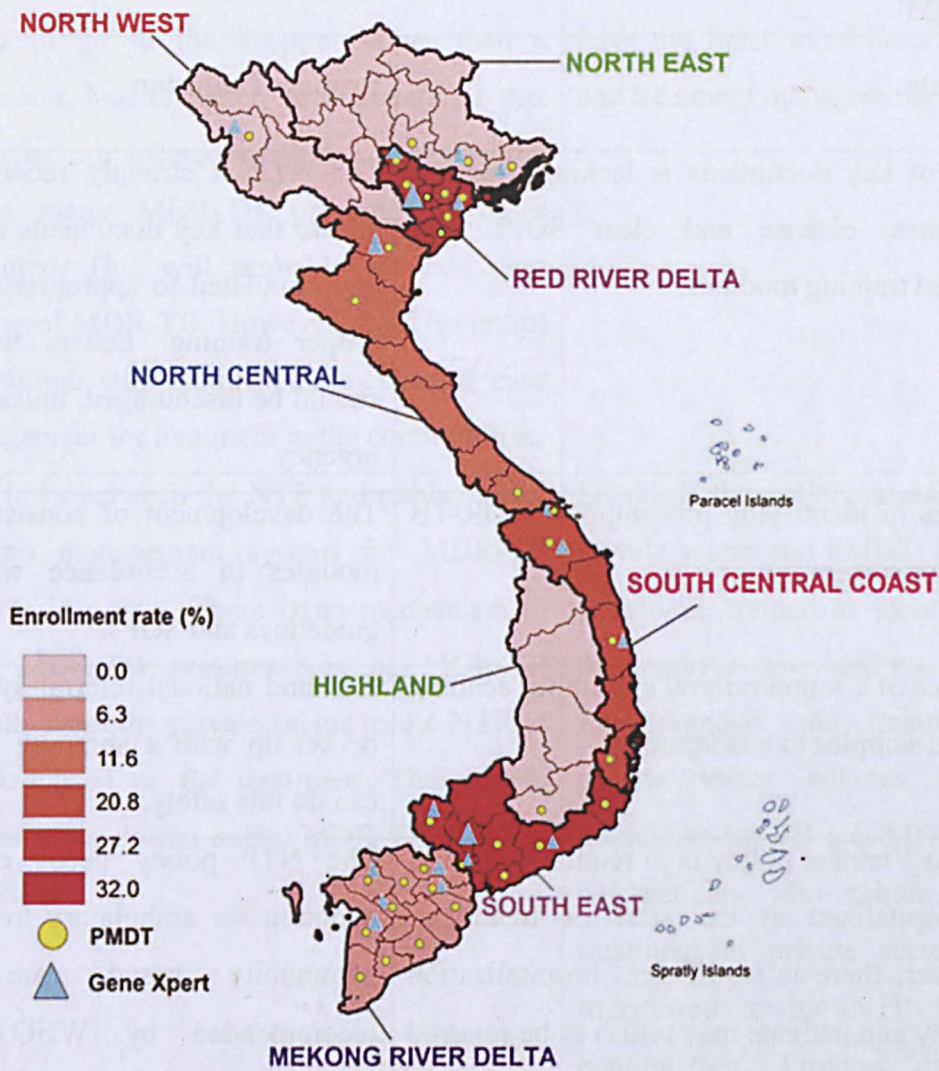
4.3.5 Qualitative investigations (all steps)

This section reveals the challenges to a successful diagnosis and enrollment for treatment of MDR-TB (Table 4-4). It was noted that TB units (i.e. small departments operating under the NTP that identify MDR-TB presumptive, provide TB diagnostic and first-line treatment services by specifically trained staff) are located mainly in district health centers. Although there is a policy change ongoing to have TB units also in (district) hospitals this had not yet been implemented in all districts. As a result, several district hospitals, where many MDR-TB presumptive cases present did not have TB diagnostic facilities and hospital staff had not been trained and instructed to screen patients for TB and MDR-TB.

Table 4-4. Obstacles to enrolling MDR-TB patients for treatment and solutions for an effective PMDT

Ser. No	Obstacle	Proposed solution
1	A set of key documents is lacking: updated guidelines, concise and clear SOPs, and standard training modules.	The NTP is strongly recommended to ensure that key documents are prepared and circulated to appropriate staff, with proper training. Letters with updates should be discouraged, unless there is an urgency.
2	Failures in identifying presumptive MDR-TB cases for screening.	The development of consistent training modules in accordance with national guidelines and SOPs.
3	Absence of a sound referral system for sending sputum samples to a laboratory.	A sound national referral system should be set up with a shipping agency who can do this safely.
4	Current Vietnam policy is to require patient to be hospitalized at the start of treatment. However, there is insufficient hospitalization capacity and patients may refuse to be referred to another treatment centre in another province either due to distance from hometown or additional costs without getting health insurance reimbursement.	The NTP policy needs consider the adoption for ambulatory treatment with community based care as also recommended by WHO [8]. Health insurance need to support MDR-TB patients in reimbursing costs in case there is a need for referral to another province for PMDT treatment.
5	Temporary MDR-TB drug stock-out due to procurement and distribution delay resulted in patients either not enrolled for treatment or a delay in treatment.	Improve drug procurement and distribution system.
6	TB units in many districts remain located in health centers that focus on prevention, and are separate from the general hospitals, which	Enforce policy to locate TB units in the district general hospitals. Training should be provided to appropriate staff

	is discrepant from MoH policy. As individuals prefer to go to the hospital rather than a preventive health center, it is beneficial that TB units are located in the district hospital where many MDR-TB presumptive cases presented. This will probably increase case finding of MDR-TB. However, the TB control programme still requires a function of case management for treatment in the communities.	to ensure that TB units in the hospital have the function of both TB diagnosis and treatment management.
7	Poor links between the NTP and public sector and no management system for MDR-TB patients in prison. There is no mechanism to refer MDR-TB presumptives or MDR-TB patients from the private sector to the NTP to be diagnosed or for treatment. The private sectors often do not notify MDR-TB cases to the NTP.	Establish the collaboration between the private sector and PMDT. Private sector should be trained to identify MDR-TB presumptive cases and refer to the NTP for diagnosis and treatment. Ensure private sector adheres to treatment guidelines for TB and MDR-TB. MDR-TB patients who cannot. to continue treatment in private sector should be transferred to the NTP for treatment continuation. Provide diagnosis and treatment service for MDR-TB patients in prison.

Provincial and district staff reported that they were overall not well informed about PMDT procedures. The first guideline for PMDT was issued in 2009 [11] and has not been updated for any of the multiple changes since then. The changes in policies over time had been updated through separate instruction letters from the central level and though yearly PMDT training courses without documenting these in a clear set of guidelines. A total of 17 instruction letters to inform about changes have been sent out from central level to provinces between 2009 to late 2013. However, regularly these update letters were not received by the provincial PMDT officer or the information was not disseminated to the relevant staff at lower levels. A further challenge

was regular health care staff turnover or change in health care staff's responsibilities over time. As a consequence, it is challenging to ensure training and skills development for all the staff involved in TB and MDR-TB management.

Standard operating procedures (SOPs) for PMDT were developed and released in 2012, three years since the MDR-TB guideline was released. The SOPs lacked clear instructions for steps that need to be taken [16]. No standard PMDT training modules are available as the training and presentations were prepared and updated by different lecturers, based on their interpretation of the available guidelines and SOPs. Inconsistencies across training courses were mentioned by trained health staff, which generated uncertainty. In addition, the majority of district level staff was not trained due to lack of funding. In 2013, the majority of district staff with an assigned responsibility to identify presumptive MDR-TB had not been trained to identify risk groups. Supervision visits conducted between April and July 2014 revealed that, although all districts under PMDT had been trained, their focus was on retreatment cases, while non-converters among new cases and HIV-positive TB patients were generally neglected.

Many TB units were unable to send sputum for testing by Xpert MTB/RIF as no appropriate financial compensation mechanisms were in place for consumable procurement and sputum transportation fees. Partly this was due to a delay in an award from the Global Fund. In addition it was not straightforward to send specimens by mail as no agreements with the postal services were in place, and sputum referral using health staff or public transportation were used instead. This may explain why in some regions with Xpert MTB/RIF capacity, like the Mekong delta region, the proportion tested and enrolled was limited. Finally, there had been stock outs of Xpert MTB/RIF test kits due to delays in cartridge forecast reporting. Although challenges were mentioned for sending sputum, there was always a confirmation and communication between referring sites and laboratory after samples had been sent. A small number of referred samples were rejected by the laboratory for being considered low-quality or low-volume, and requested to re-collect and re-send.

For MDR-TB patients that were diagnosed, health staff mentioned that informed consent was obtained for all of these patients before starting treatment. There were issues regarding enrolling MDR-TB patients for treatment due to lack of hospitalization capacity. It was reported that poor links existed between the public and private sector, as patients cannot be referred from the

private to the public sector to continue their treatment. Furthermore, there are no management systems in place to screen and treat MDR-TB patients in prison (see Table 4-4 for more details).

4.4 Discussion

We estimated that only one third of MDR-TB presumptive cases are screened by Xpert MTB/RIF in Vietnam. However, it is encouraging that 95 % of the patients who were tested positive for MDR-TB were enrolled for second-line treatment. The low enrollment rate is mainly attributable to low number of presumptive MDR-TB cases identified and subsequently tested, and not due to poor enrollment of patients after diagnosis. There were some inconsistencies between the percentage of MDR-TB presumptive cases tested in 35 PMDT provinces (Table 4-2) and the enrollment rate of MDR-TB (Table 4-1). While there were relative high testing proportion in the North-East, North-West, Northern Central and Southern Central Coast regions, the enrollment proportion for treatment among number estimated were low, varying from 0 % to 27.3 %. In other regions, the variations in enrollment rates were in line with the variations in percentage of MDR-TB presumptive cases tested. The reasons behind these inconsistencies were limited capacity for hospitalization and other issues as revealed by our qualitative assessment.

This study showed that access to Xpert MTB/RIF testing was overall sufficient for Vietnam. However, regions with a higher number of operational Xpert MTB/RIF instruments had a higher enrollment proportion compared to regions with fewer instruments, except for the Mekong River Delta (Figure4-3). While the burden of MDR-TB in Mekong Delta region was high, with Xpert MTB/RIF instruments widely available, the enrollment proportion in this region was very low: 7.5 % (Table 4-1, Figure4-3). The reason behind the low enrollment proportion in Mekong Delta region is a weak system for transferring specimens for Xpert MTB/RIF testing as revealed by our qualitative study. In addition, procurement of test kits needs improvement to avoid stock outs, and redistribution of Xpert MTB/RIF instruments from the Red River Delta with 9 instruments and a low workload to the Northern Central region with just one instrument and a high workload may improve access to testing for risk categories. Testing coverage was nil in the Central Highlands region. Although this area has a relatively low number of estimated MDR-TB cases, facilitating a good specimen referral system for testing could increase the coverage. Main

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challenges for effective MDR-TB diagnosis and treatment and potential solutions proposed by our study team for under enrollment are listed in Table 4-4.

New TB patients whose sputum had not converted after 2 or 3 months of treatment and TB patients with HIV, both considered risk groups for MDR-TB, were largely neglected for screening and had the lowest proportions of MDR-TB screening done while they account for the majority of presumptive MDR-TB cases [8][11]. Since the proportion of detected rifampicin-resistant patients among these groups in 2013 was 11.3 % [9], it is likely that a considerable number of MDR-TB remain undiagnosed due to inadequate screening among these groups. Importantly, undetected MDR-TB/HIV patients who have high mortality rates [1] [14] would lose the opportunity for adequate treatment. Moreover, TB-HIV patients in 2013 are underreported due to limited collaboration between the TB and HIV control programs [2].

The qualitative assessment revealed that many patients refuse treatment in units far from home. Other patients reported problems getting health insurance reimbursement in case they were referred to another province. Lack of collaboration between treatment centers and adjacent provinces for referring patients for treatment also contributed to drop outs. Another contributing factor to treatment delays and poor enrollment was the irregular delivery and stock outs of MDR-TB treatment drugs due to procurement delays. Occasionally, patients insisted to be enrolled, but they had to wait for a long time to start treatment.

This study also revealed poor links between the public and private sector. Due to absence of a referral mechanism between the two systems, MDR-TB presumptive were not referred from private sector to the NTP for diagnosis, and patients who withdrew from MDR-TB treatment in the private sector for financial or other reasons were unable to enroll to continue treatment in the public PMDT. Currently, only limited data for MDR-TB patients in the private sector are available, where default rates are high, up to 75 %, implying poor MDR-TB management in the private sector that may lead to drug resistance amplification [13]. Also MDR-TB patients in prisons pose a challenge as second-line treatment is not available, and no procedures for management of MDR-TB patients after discharge from prison are in place.

The current PMDT policy is that each district should have a TB unit. The Ministry of Health has as a policy to locate TB units in general hospitals, or in district health centers if a general

hospital is not present [3]. This policy is aimed at strengthening the utilization of diagnosis and treatment services for TB units in the district hospital, where most patients seek health care. However, our study found that not all district hospitals have a TB unit with TB screening capacity. Health staff lack proper training and MDR-TB screening skills and do not have access to updated guidelines/SOPs to support them in identifying patients. This results in confusion and limited confidence among staff to implement the PMDT properly. Inconsistencies across training courses also contributed to confusion around the PMDT policies. Clear guidelines, instructions and training for health staff is needed to improve this.

Our study has several limitations. To estimate the MDR-TB enrollment proportion we used two different data sets: the 2013 NTP report and the DRS conducted in 2011–2012. For the number of MDR-TB cases detected, we only used laboratory reports from Xpert MTB/RIF testing and we did not include reports from other tests such as line-probe assays or phenotypic drug susceptibility testing. As the number of tests done by these other methods is small, less than 5 % with considerable overlap with Xpert MTB/RIF testing, we decided to exclude these.

Furthermore, as we do not know the prevalence of rifampicin resistance for each MDR-TB risk group we could not assess the positive predictive value (PPV) of Xpert MTB/RIF separately among each category of presumptive MDR-TB patients. However, for most categories, the estimated prevalence of rifampicin resistance is relative high (around one-fourth, given the 23 % prevalence among previously treated patients in the DRS). In addition, recent studies from South Africa [12] and Brazil [17] suggest a PPV on the order of 90 % even with relatively low prevalence of rifampicin resistance. Therefore we do not expect that the PPV in our study will have been much below 90 %, and thus did not affect the results to considerable extent.

A final limitation is that we did not involve the private sector in our study. However, our qualitative assessment suggests poor management of MDR-TB in the private sector and a lack of a good referral system between the private and public sector. This situation causes patients to be under screened, poorly treated, and underreported to the NTP. Better links need to be established between the private and public sector.

4.5. Conclusion

The proportion of MDR-TB patients enrolled for second-line treatment among the total estimated number of MDR-TB cases in Vietnam in 2013 was 18.7 % (948/5065). The low enrollment was considered due to under-screening of MDR-TB presumptive cases, especially for HIV infected and new TB non-converters. Multiple reasons exist for under-screening, including: poor communication and implementation of policy changes, lack of involvement of general district hospitals, and limited resources. However, Vietnam has achieved a high proportion of enrollment to second-line treatment among of detected MDR-TB cases and a high treatment success rate, which can be considered an opportunity to mobilize resources and expand the program to detect and treat more MDR-TB cases. Vietnam should expand the intensified case finding of MDR TB by a comprehensive strategy with more focus on new detected cases, in particular those with HIV co-infection and contacts of MDR-TB patients. The capacity to treat new MDR-TB cases will need to be increased in case the screening is improved. The private sector needs to be engaged in the PMDT.

References

1. World Health Organization. Global tuberculosis report 2014. Geneva, Switzerland: WHO; 2014. WHO/HTM/TB/2014.08.

2. National Tuberculosis Control Program of Vietnam. National Guidelines for Programmatic Management of Drug Resistance Tuberculosis. Hanoi: Ministry of Health; 2009: 1-142.

3. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland: WHO; 2008.WHO/HTM/TB/2008.402

4. World Health Organization. Global tuberculosis report 2013. Geneva, Switzerland: WHO; 2013. WHO/HTM/TB/2013.11

5. World Health Organization. Global tuberculosis report 2012. Geneva, Switzerland: WHO; 2012. WHO/HTM/TB/2012.6

6. C. Nagaraja, B. L. Shashibhushan, M. Asif, M. Ph, and C. Sagar. Pattern of Drug-resistance and Treatment Outcome in Multidrug-resistant Pulmonary Tuberculosis. Indian J Chest Dis Allied Sci. 2012 Jan-Mar; 54(1):23-6.

7. R. M. Falzon D1, Jaramillo E, Wares F, Zignol M, Floyd K. Universal access to care for multidrug-resistant tuberculosis: an analysis of surveillance data. Lancet Infect Dis, 2013, 13(8):690-7. doi: 10.1016/S1473-3099(13)70130-0. Epub 2013 Jun 4

8. World Health Organization. Rapid Implementation of the Xpert MTB / RIF diagnostic test, Technical and Operational "How-to", Practical consideration. Geneva, Switzerland: WHO; 2011. WHO/HTM/TB/2011.2

9. National Tuberculosis Control Program of Vietnam. Standard Operational Procedure for Programatic Management of Drug resistant Tuberculosis in Vietnam. Hanoi: Ministry of Health; 2012: 1-86

10. National Tuberculosis Control Program of Vietnam. Laboratory performance report from National TB control programme of Vietnam. Hanoi: National Reference Laboratory; 2013. Ref Type: Report.

11. Finlay AF. Treatment outcomes of patients with multidrug resistant tuberculosis in South Africa using a standardized regimen, 1999–2000. Infectious Disease Society of America (Poster session 58, N_ 2101). Boston, MA, September 2004.3.

12. Park MM, Davis A L, Schluger N W, Cohen H, Rom WN. Outcome of MDR-TB patients, 1983-1993. Prolonged survival with appropriate therapy. Am J Respir Crit Care Med 1996, 153(1):317–324.

13. National Tuberculosis Control Program of Vietnam. Annual review meeting report of the National TB Control Programme of Vietnam, 2013. Hanoi: National Tuberculosis Control Programme of Vietnam; 2013. Ref Type: Report.

14. Pandey S, Quelapio M, Hennig C, Khanh PH. Green Light Committee Monitoring Mission Report for Vietnam. The Philippines: World Health Organization -Western Pacific Regional Office; 2013: 1-73

15. Ministry of Health of Vietnam. Approving the development plan for tuberculosis and lung diseases control network, period from 2011-2020. Hanoi: Ministry of Health; 2011: 2357/QĐ-BYT.

16. Osman M, Simpson J, Caldwell J, Bosman M, Nicol MP. GeneXpert MTB/RIF version g4 for identification of rifampin-resistant tuberculosis in a programmatic setting. J. Clin. Microbiol. 2014; 52(11): 635-637

17. Trajman A, Durovnil B, Saraceni V, Cordeiro M, Cobelens F, van den Hoff S. High positive predictive value of Xpert in a low rifampicin resistance prevalence setting. J. Ersjournal. 2014; 44(6): 1711-1713

Chapter 5. CONTACT TRACING BY SOCIAL NETWORK ANALYSIS (SNA) TO ENHANCE MULTI-DRUG RESISTANT TUBERCULOSIS CASE FINDING IN HANOI, VIETNAM

5.1 Introduction

The emergence of resistance to anti-tuberculosis drugs, and particularly of multidrug-resistant TB (MDR-TB) is a serious public health threat and an obstacle to effective global TB control [1]. Inappropriate or incorrect use of anti-TB drugs, or use of poor quality medicines, weak health systems, social determinants are the main cause of drug resistance development and spread [2]. In the world, about 3.5% of new TB cases and 20.5% of previously treated cases have MDR-TB strains. Only 20% of estimated MDR-TB cases are reported to be on recommended treatment with a success rate of just 48% [3]. In this context, the Stop TB Partnership Global Plan aims that by 2015 at least 75% of MDR-TB cases need to be treated successfully [4] In order to achieve these targets, it is crucial to identify more MDR-TB cases at an earlier stage and provide optimal treatment.

Viet Nam is ranked 14th among 27 high burden MDR-TB countries [2]. To meet the targets set in the Global Plan to stop TB, Viet Nam has approved the plan to detect and treat more MDR-TB cases, reaching 1,115 cases in 2014. As of September 2009, Viet Nam has started to implement Programmatic Management of Drug Resistance Tuberculosis (PMDT), the main component for TB control. By 2012 Viet Nam has adopted the use of Xpert MTB/RIF for detection of MDR-TB cases in PMDT sites and set up mechanism to access second line drugs (SLDs) for MDR-TB patients. Chapter 2 on MDR-TB control policies and practices in Vietnam of this thesis presented details on MDR-TB case finding strategies to meet the target.

Despite these efforts in Viet Nam, the proportion of MDR-TB cases detected and enrolled to treatment annually compared with the estimated of MDR-TB cases among notified TB cases is low (less than 30%) [5], leaving the majority of undetected MDR-TB to persist in the community. The existence of drug-resistant strains in a population is an important source of transmission for new drug-resistant cases. In addition, the majority of MDR-TB found among new cases (patients who never received TB treatment before) in Viet Nam suggests that community based transmission an important source of new MDR-TB cases. Among the total of 5,100 MDR-TB estimated cases, there are about 3,000 (58.8%) with new pulmonary MDR-TB

and 2,100 (41.2%) previously treated TB cases [3]. The existing MDR-TB case finding strategy of PMDT in Viet Nam focuses on screening drug resistance among previously treated cases, or patients currently on TB treatment who are non-converter, failed treatment, or relapsed and not among new TB cases.

Household contacts are classified as a risk group but currently undergo a passive case finding approach, i.e. they are advised to seek help in when symptomatic. Data from our prevalence survey conducted in 2006-2007 showed that this existing passive case finding approach can only detect about 60% of patients, leading to the recommendation to conduct an active case finding approach in risk groups [6]. Our study on household contact investigation also shows a low proportion of contacts screened with a passive approach (Chapter 3) [7].

Although close contacts of MDR-TB patients are recommended by the National Tuberculosis Control Programme (NTP) of Viet Nam to be screened for MDR-TB [8], there is not yet a clear mechanism for contact tracing in Viet Nam. Recently, one study that used population-based data from rural Viet Nam showed that only 1% of index cases have a TB positive household member and 83% of these household TB cases have a different strain of *M. tuberculosis* compared to their household members. This finding suggests that most TB cases result from transmission outside the household [9]. These results are similar to those in high incidence settings in South Africa, and Malawi [10][11].

Traditional contact tracing can only identify a few instances of transmission and often only focuses on household contacts and little on other common contacts at for example work, school, or social contacts [12][13][14]. Contact investigation of only household members is not sufficient to identify the transmission of MDR-TB and additional approaches are needed. It is also recommended by the WHO that, to conduct investigation among contacts of MDR-TB and XDR-TB, additional information should be collected regarding description of their residence and other sites where transmission might have occurred [15].

Social network Analysis (SNA) is a more comprehensive approach than traditional contact tracing which includes a set of persons (nodes) and the connections (ties) among them for analysis of structure of disease transmission. The basic unit of analysis in SNA is the tie linking at least two nodes (e.g., person to person or person to place dyads). It measures the nature of

these connections such as work- or school-associated activity, kinship within a network [16][17]. These contacts and places are identified through the structure of social network based on the links between at least two MDR-TB cases. In identifying a probable source case and locations targeted for follow-up, social network analysis is supposed to be able to outperform standard contact tracing [18].

Screening for MDR-TB among contacts is an important priority for effective TB control. We conducted this study to assess the yield of social network investigation among contacts of MDR-TB patients in case detection of MDR-TB in Viet Nam. Additionally we looked at feasibility of such an active contact investigation strategy among contacts of MDR-TB patients in Viet Nam. This is a preliminary analysis as the study is still ongoing.

5.2 Methods

We used a mixed methods approach. To analyze the detection rate of an active social network approach we conducted a cohort study in which we followed up close contacts and household contacts of MDR-TB patients over a period of at least 6 months. To look at feasibility of this approach, we organized a workshop to distribute semi-structured questionnaires to be self-completed by TB health staff who participated in the contact investigation activities of the study. The questionnaire was followed by an open discussion for to discuss experiences and challenges that were encountered when performing MDR-TB social network analysis. The study protocol was reviewed and approved by the Science and Ethical Committee of the Viet Nam National Lung Hospital (Code 388/2013/NCKH).

5.2.1 Cohort study

MDR-TB patients who lived in Hanoi and diagnosed as MDR-TB between October 2013 and April 2015 were eligible for the study. After informed consent was obtained, the predesigned and pilot validated case report form (CRF) was used to interview MDR-TB patients to collect the following data: demographics, medical history, social network including their contacts and frequently visited places (see appendix for CRF). The interviews were conducted by trained TB healthcare workers as soon as MDR-TB patients were diagnosed. Completed CRFs of MDR-TB patients were submitted to central level as soon as completed to identify the places and contacts need to be investigated including checking whether similar contacts or places have been reported by other MDR-TB patients.

MDR-TB contacts were followed up at district level by the study team to undergo MDR-TB screening after informed consent was obtained. Eligible places (the recommended places for screening as described in definitions) were also accessed and investigated by provincial or district coordinators to identify additional contacts for MDR-TB screening using an interview guide. The contacts screening for TB and MDR-TB involved (i) clinical assessment to identify presumed TB patients and people at risk of MDR-TB using predesigned CRF, (ii) chest X ray to identify presumed TB patients (abnormal chest X-ray suggested for TB) among those who were not presumed by clinical assessment, and (iii) microbiology (Xpert MTB/RIF) to identify TB and rifampicin resistant TB among those who are identified as presumed TB patients either by clinical assessment or chest X-ray (refer to screening steps for more detail). Contacts diagnosed as TB or MDR-TB cases will be treated according the current TB treatment guidelines in Viet Nam. MDR-TB treatment is made available free of charge in Viet Nam. Field visits to supervise the study implementation were conducted quarterly from central and provincial level to district level.

5.2.2 Study population

The study involved patients detected with rifampicin resistant TB (either diagnosed by Xpert MTB/RIF or by Hain test, the test that were being used by the NTP for MDR-TB diagnosis) and their eligible contacts (all ages), who were named by index patients or identified from places and able to give informed consent. In case the patient was unable to answer the questions, a family member who is expected to know the individual best, was asked to answer on his/her behalf.

Inclusion Criteria: The study included rifampicin resistant TB or MDR-TB patients living in Hanoi (all ages) who are diagnosed (either diagnosed by Xpert MTB/RIF or by Hain test) and put on MDR-TB treatment between October 2013 and April 2015. Additionally, their defined contacts (either named by patients or came from eligible places) during 3 months preceding MDR-TB diagnosis were also included in the study. Only participants who were willing and able to give informed consent for participation were selected for screening. For patients and contacts who are children (less than 18 years old), information was obtained from their parents or responsible family members.

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Exclusion Criteria: Cases or contacts were excluded if no informed consent was obtained. Index MDR-TB patients who were diagnosed and enrolled for treatment in Hanoi, but lived in other provinces before coming to Hanoi for diagnosis and treatment could not enter the study. Contacts with the index MDR-TB cases not during 3 months prior to MDR-TB diagnosis were also excluded.

5.2.3 Follow up

There were two active screening moments in this study. The first was at the time the eligible contacts were identified and the second at 6 months post MDR-TB diagnosis. Eligible contacts were recorded in a registered book to be followed up by district coordinators. The second screening was made by an appointment on completion of the first active screening, and followed by a reminder at 6 months by telephone. During the study period, study participants were asked to make an unscheduled visit to district TB units and contact with the district health coordinators if they had any symptom suggestive of TB.

Screening steps and diagnostic testing included (see Figure 5-1):

- Clinical assessment by trained district health coordinators to identify MDR-TB presumptive cases , which included: (i) eligible contacts with productive cough for more than 2 weeks, which may be accompanied by other symptoms, (ii) TB patients who were on current first line anti-TB treatment initiated before being identified as eligible contacts of MDR-TB, (iii) children with failure to thrive, two weeks of fever or cough, or cervical lymphadenopathy.

- Chest X-ray to detect additional MDR-TB presumptive cases among those who were not identified as MDR-TB presumptive case by clinical assessment alone. This examination was taken at district health facilities. MDR-TB presumptive cases were identified in case of an abnormal chest X-ray suggestive of TB.

- Xpert MTB/RIF testing to detect TB and rifampicin resistant TB. This was done among MDR-TB presumptive cases who were either identified by clinical assessment or by chest X-ray. Microbiological testing was done on sputum or gastric aspirates in children.

Figure 5-1. Recruitment and screening process among close contact of MDR-TB index patients

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                          ┌──────────────────┐
                          │ Eligible contacts │
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                                   │
                                   ▼
                          ┌──────────────────┐
                          │    Interview      │
                          └──────────────────┘
                                   │
                   ┌───────────────┴───────────────────┐
                   ▼                                     ▼
        ┌────────────────────────┐          ┌──────────────────────────┐
        │ TB suspects by interview│         │ Not TB suspects by interview│
        └────────────────────────┘          └──────────────────────────┘
                   │                                     │
                   │                                     ▼
                   │                          ┌──────────────────────┐
                   │                          │  X-ray examination    │
                   │                          └──────────────────────┘
                   │                              │              │
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                   │                    ┌────────────────┐  ┌──────────────┐
                   │                    │ Abnormal X-ray │  │ Normal X-ray │
                   │                    └────────────────┘  └──────────────┘
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                   │                    │ TB suspects by │  │  Not TB      │
                   │                    │    X-ray       │  │  suspects    │
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                   │                              │              │
                   └──────────────┬───────────────┘              ▼
                                  ▼                     ┌──────────────┐
                    ┌────────────────────────┐          │ Consultation │
                    │   Gene Xpert MTB/RIF     │         │  Follow-up   │
                    └────────────────────────┘          └──────────────┘
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TB (+)/R(+)	TB (+)/R(-)	Negative
Second line drugs treatment Culture, DST	First line drugs treatment Follow up, can repeat Xpert after 2 months if sputum not converted	Consultation Follow up

Operational definitions (see Appendix 2 for more detail)

MDR-TB presumptive case: In this study, the MDR-TB presumptive referred to any MDR-TB contact with (i) clinical symptom suggested for TB or (ii) abnormal findings consistent with TB on the Chest X-ray (CXR) or (iii) TB patients who were on current first line anti TB treatment.

Multidrug-resistant tuberculosis (MDR-TB) case: defined as TB caused by strains of *Mycobacterium tuberculosis* that are resistant to at least isoniazid and rifampicin. In this study, patients who are tested by Gene-X-pert and are positive for rifampicin resistant TB will be also classified as MDR-TB (because more than 96% of rifampicin resistance in Vietnam is also resistant to isoniazid).

Index MDR-TB case: rifampicine resistant or MDR-TB patient who was diagnosed and enrolled to treatment by routine system.

Household contact: all household members of the MDR-TB patients, including children who should have been in the household at least 4 hours a day, for at least 14 days, or a cumulative total average exposure of at least 8 hours per week for at least 8 weeks during 3 months leading up to the time of TB diagnosis.

Close contact: any individual apart from household members who also have frequent and prolonged contact with the MDR-TB patients (i) in in-house environment during 3 months leading up to the time of TB diagnosis, (ii) spend at least 4 hours a day, for at least 14 days, or a cumulative total average exposure of at least 8 hours per week for at least 8 weeks together with the patient in in-house environment.

Mutual contact: a contact that is named by at least 2 confirmed MDR-TB patients.

Mutual place: a place that is named by at least 2 confirmed MDR-TB patients.

High risk place: The in-house condition place where the MDR-TB index case spend an average of at spend at least 4 hours a day for at least 14 days, or a cumulative total average exposure of at least 8 hours per week for at least 8 weeks in 3 months prior MDR-TB diagnosis.

Eligible place: includes mutual places and high-risk places.

Eligible contact: Includes (i) household contacts, (ii) close contacts, (iii) mutual contacts, (iv) people who frequently visited the eligible places during 3 months leading up to MDR-TB diagnosis and found to be TB suspects by primary interview.

5.2.4 Sample size

It was estimated that one index MDR-TB case would have approximately 3 eligible contacts. It was expected that 75% of contacts will be screened. It was assumed that 10% of the contacts will be symptomatic of which 15% will have TB and 60% of TB will be MDR. Therefore, the yield of contact tracing by SNA to MDR-TB case detection for 100 index cases was estimated to be 2.0% (2 cases per 100 index cases). The minimum sample size we needed in order to detect the estimated yield of active case finding of 2 cases per 100 index cases with 95% CI significantly different from 0 is 100 as shown in table 5.1

Table 5-1. Sample size calculation.

Index patients recruited (n)	Estimated eligible contacts enrolled (n)*	Contacts with active TB (n)**	Expected point estimate for proportion of contacts with TB (%) ***	Estimated 95% confidence limits	
				lower	Upper
200	600	4	2.0	0.6	5.0
200	600	3	1.5	0.3	4.3
100	300	3	3.0	0.6	8.5
100	300	2	2.0	0.2	7.0
100	300	1	1.0	0	5.5
50	150	3	6.0	1.3	16.5
50	150	2	4.0	0.4	13.7
50	150	1	2.0	0	10.6

*Based on assumption of 3 contacts screened per index patient. **Assumption for number of contacts diagnosed as active TB. *** Number of patients detected by SNA divided by number of index cases

5.2.5 Data analysis

All CRFs were collected, screened and entered into data entry platform using MS Access software (Microsoft Inc, USA). Data were then transferred to SPSS 16.0 for statistical analysis. MDR-TB detected among close contacts was calculated to compare to that from current passive case finding strategy. Descriptive statistics, including frequency, median, interquartile range (IQR), proportion and 95% confidence intervals (95% CIs), were performed where appropriate. The comparisons were tested statistically using Chi-Square test to compare proportion. P-values (2-sided) below 0.05 were considered significant.

5.2.6 Qualitative assessment

In July 2015, a one- day workshop was conducted among 26 key staff members who were involved in the study in order to obtain information on their experience in implementation of investigation among contacts of MDR-TB patients in Viet Nam. These include 18 doctors and assistant doctors at 18 district TB units, 5 study coordinators working at provincial TB programme who were involved in interviewing MDR-TB patients, supervisions for study implementation at district level, and 3 staff from the National TB Control Programme. All staff were invited to the workshop and were given a semi-structured questionnaire to be self-completed by them. District TB staff were asked about the project progress at their location, list down key steps in the SOP on contact investigation of the research, identify challenges and propose solutions in contact investigation. After a break the moderator summarized key findings from the questionnaire, followed by an open discussion among all 26 staff to understand the problem they had when conducting contact investigation. After the workshop, the moderator reviewed and summarized key findings noted form the questionnaires.

5.3 Results

5.3.1 Characteristic of MDR-TB patients (index cases) and their contacts.

Characteristic of MDR-TB patients

A total of 99 MDR-TB index cases were enrolled into the study including 77 and 22 patients diagnosed by Xpert MTB/RIF and Hain test, respectively. The majority of MDR-TB patients belong to the age group 35-54 years old. Male to female ratio was 3.5:1, and 4% (95% CI: 0.2%-7.9%) of MDR-TB cases were HIV positive.

Table 5-2. Characteristic of patients at baseline

Characteristic		n	%
	Total patients		
Age group	0 – 14 years	0	0.0
	15 - 24 years	14	14.0
	25 - 34 years	15	15.0
	35 – 44 years	29	29.0
	45 - 54 years	23	23.0
	55 – 64 years	14	14.0
	65 year and above	5	5.0
	Median age	43	
	Mean age (sd)	42.3 (13.9)	
Gender	Male	78	78.0
	Female	22	22.0
HIV (+)		4	4.0

Test results of patients at baseline

Sputum smear and chest X-ray were performed for 99 MDR-TB patients: 76/99 (76.8%; 95% CI:68.5%-85.1%) had a smear- positive result. Approximately 30% of MDR-TB patients had evidence of cavity manifestation on chest X-ray (Table 5-3).

Table 5-3. Test results microscopic smear and chest Xray of MDR-TB index patients at enrollment.

		n	%
Sputum smear	**Total smear taken**	99	100.0
	Negative	23	23.2
	Positive	76	76.8
Grade among smear positive[a]	Scatter	20	26.3
	1+	33	43.4
	2+	13	17.1
	3+	10	13.2
Chest X-ray	**Total chest Xray taken**	99	
	Cavity	32	32.3

[a]*Based on the International Union Against Tuberculosis and Lung Disease (IUATLD)-recommended grading of sputum smear microscopy results*

Categories of MDR-TB patients

More than 70% of MDR-TB patients were previously treated cases and non-converters of retreatment regimen with first line anti TB drugs. Only 14% of patients belonged to new category (Table 5-4).

Table 5-4. Categories of MDR-TB patients

Patient category	n	%
New	14	14.1%
Non-converters of first line drug for new cases	11	11.1%
Non-converters of first line drug for retreatment cases	1	1.0%
Previously treated cases	69	69.7%
Others	4	4.0%
Total	99	100.0%

5.3.2 Characteristics of contacts

There were a total of 496 contacts of the 99 index MDR-TB patients. The number of contacts excluded from the study before conducting social network analysis was 79 (15.9%). Most excluded contacts composed of contacts who were not living in Hanoi and/or not met the index patients during 3 months up to the time of MDR-TB diagnosis. Characteristics of eligible contacts are described in Table 5-5. The identified 417 (84.1%) contacts were eligible to enter the study, including: 292 (70%) household contacts and 125 (30%) non- household contacts. Of 125 outside household contacts, one contact came from a high-risk places. The male-to-female ratio was approximately 1:0.8. Of 417 eligible contacts, 86 (20.6%) were children under 14 years of age at the time of the identification.

Table 5-5. Characteristics of MDR-TB eligible contacts

Characteristic		n	%
	Total contacts	**417**	
Age group	0 – 14 years	86	20.6
	15 - 24 years	65	15.6
	25 - 34 years	65	15.6
	35 – 44 years	67	16.1
	45 - 54 years	49	11.8
	55 – 64 years	50	12
	65 year and above	27	6.5
	Missing	8	1.9
	Median age	32	
	Mean age (sd)	34.0 (20.0)	
Gender	Male	189	45.3
	Female	223	53.5
	Missing	5	1.2
Type of contact	Household contact	292	70
	Outside household contacts	125	30

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Figure 5-2. Contacts of MDR-TB identified and participated in the screening
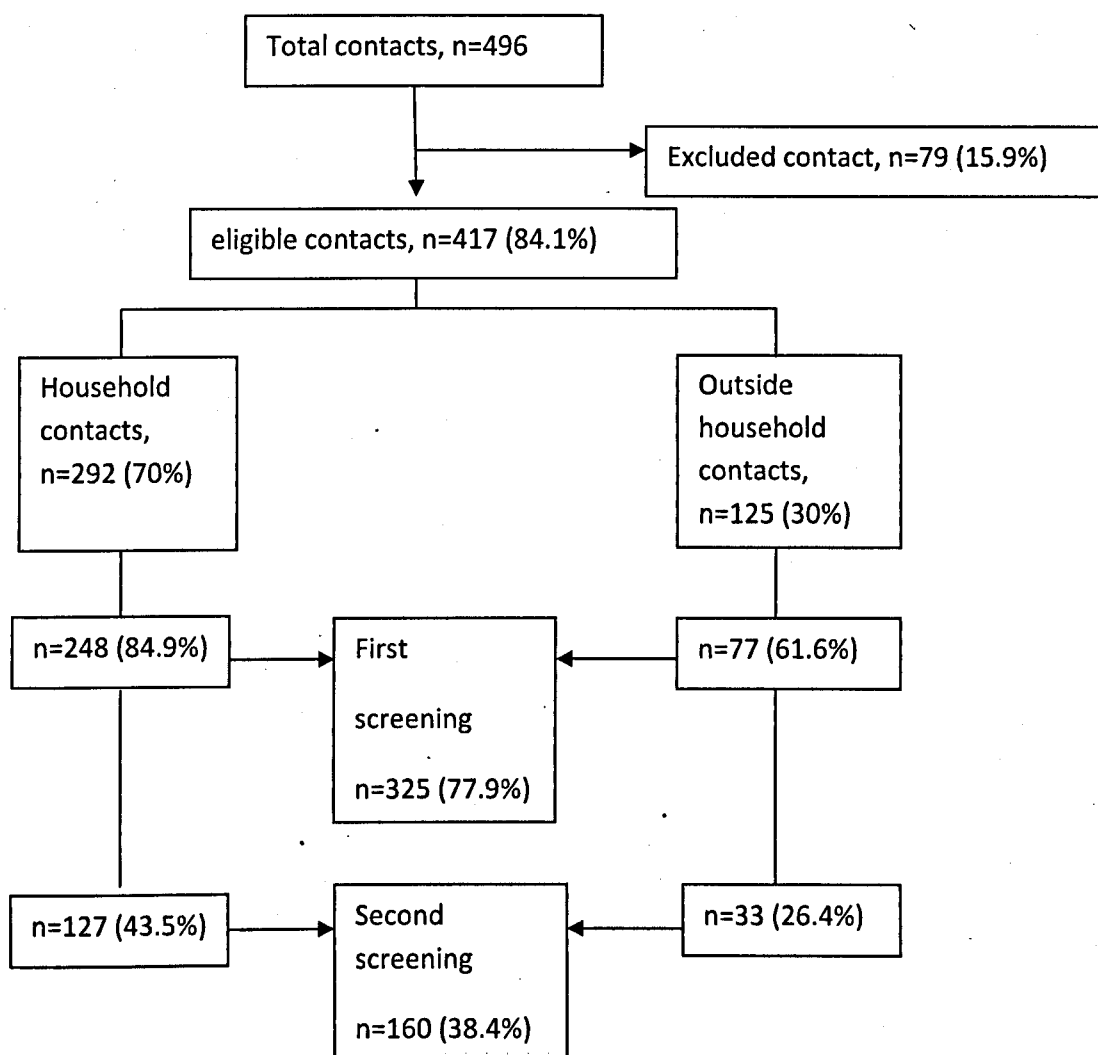
5.3.3 Screening practices

Of the recruited 417 contacts, 325 (77.9%) contacts participated in the first screening. The household contacts and non-household contacts that participated in the first screening were248/292 (84.9%; 95%CI:80.8%-89.0%) and 77/125 (61.6%; 95%CI:53.1%-70.1%), respectively. Participation in the second screening among eligible contacts, household and outside household contacts was only 160/417(38.4%), 127/292 (43.5%; 95%CI: 37.8%-49.2%), and 33/125 (26.4%; 95%CI:18.7%-34.1%), respectively (Figure 5-2). Among 412 eligible contacts, the participation of female contacts in the first screening was higher than for males,

186/223 (83.4%; 95%CI:78.5%-88.3%) versus135/189 (71.4%; 95%CI:65.0%-77.9%; Table 5-6). The proportion of contacts participating in the screening was significantly different between household contacts and non-household contacts (p-value =0.0001), as well as between female and male contacts (p-value=0.003). However, there was no difference (p-value =0.139)in the proportion of contacts participating in the screening by age groups (table 5-7). Results from the first screening showed that 36/325 (11.1%) contacts interviewed were clinically assessed as presumed TB. 299 chest X-rays were performed and 12/299 (4.0%) contacts had an abnormal chest X-ray suggestive for TB. Xpert testing was provided to 48 presumed TB cases identified either by clinical assessment or by chest X-ray. We detected one TB case but not MDR-TB from the first active screening of contacts.

We were able to assess 160 contacts during the second active screening (table 5-8). 11.3% were presumed TB by interview and 9/158 (5.7%) of chest X-rays taken had signs of TB. Xpert MTB/RIF testing detected one susceptible TB case. In addition, a two-year old baby, contact with his father, was diagnosed as TB meningitis but not by our study. This baby was not identified as presumed TB in the first screening. She was taken by her parents to the national pediatric hospital and not to the district coordinator when having fever, cough and loss of consciousness. She was diagnosed as meningitis combined with pulmonary TB and put on treatment regimen containing rifampicin (her parents described her red urine after drugs taken). She died after 1 month of admission.

Table 5-6. Screening among contacts by gender

			Eligible contacts	First screening	Second screening
Gender	Male	Number	189	135	69
		% within gender		71.4%	36.5%
	Female	Number	223	186	90
		% within gender		83.4%	40.4%
	total		412	321	159

Table 5-7. Screening among contacts by age group

			Eligible contacts	First screening	Second screening
Age group	0-14	Number	86	75	45
		% within age group		87.2%	52.3%
	15-24	Number	65	53	16
		% within age group		81.5%	24.6%
	25-34	Number	65	51	27
		% within age group		78.5%	41.5%
	35-44	Number	67	51	31
		% within age group		76.1%	46.3%
	45-54	Number	49	32	14
		% within age group		65.3%	28.6%
	55-64	Number	50	40	18
		% within age group		80.0%	36.0%
	65 above	Number	27	21	7
		% within age group		77.8%	25.9%
Total			409	323	158

Table 5-8. Screening among contacts by steps

Screening steps	First active screening		Second active screening		Passive case detection	
	n	%	n	%	n	%
Interview	N = 325		N = 160		N = 25	
Presumed TB by interview	36	11.1%	18	11.3%	6	24.0%
CXR taken	N = 299		N = 158		N = 4	
Abnormal CXR	12	4.0%	9	5.7%	0	0.0%
GeneXpert taken	N = 48		N = 27		N = 6	
MTB, rifampicin susceptible	1	2.1%	0	0.0%	0	0.0%
Rifampicin resistance	0	0.0%	0	0.0%	0	0.0%
MTB, unknown resistance (*)	0	0.0%·	0	0.0%	1	16.7%

(*) Two -year old baby diagnosed as meningitis combined with pulmonary TB

5.3.4 Social network analysis

The median number of eligible contacts per index patient was 3 (IQR: 3–6). These median numbers among household and outside household contacts were 3 (IQR: 2–4) and 2 (IQR: 14), respectively. There were 35 places named by patients, of which 17 high-risk places identified to be screened. Only 1/17 (5.9%) high-risk places had participation with the owners or employers to be investigated. There was one presumed MDR-TB case identified among 15 people screened who frequented the high-risk place. We found no mutual contact and no mutual place among MDR-TB cases. There were two TB cases detected among household contact (ID 19-00-03 and ID 77-00-01) and two pairs of index cases were found to be contacts of each other (diagnosed before study started: ID 03 and 04; ID 09 and 13) (Figure 5-3).

Figure 5-3. Social network of MDR-TB cases with identified links among index cases and TB cases detected among contacts.

◆ Index MDR-TB cases	● Household contacts
● Contact case (with TB)	● Contacts outside household

🔺 High risk places: An internet cafe identified from index case ID 04. Patients spent about 10 hours per week during 3 months prior to MDR-TB diagnosis; Two beer restaurants (in-house condition) named by index case ID 09. Patient spent about 1-2 hour per day per each restaurant for every day during 2 months prior to MDR-TB diagnosis

5.3.5 Challenges and solutions for a successful implementation of contact investigation among MDR-TB patients in Vietnam

The questionnaire and discussion with healthcare workers involved in social network analysis revealed that patients' were often hesitant on being interviewed to give the information regarding their contacts. MDR-TB patients seemed not to want to reveal their contact's information because they were afraid of being noticed as MDR-TB patients. Other issues were that some districts call contacts to come to the facility rather than going to the address themselves which

lead to a higher drop out rate. Also registering and managing many contacts was administratively a challenge for centers. Another finding was that often centers did make an appointment for the second screening at the first visit. Contacts were contacted later by telephone to make an appointment. However, this practice of indirect communication may have caused that contacts were not well informed about the message and resulted in drop outs for the second screening. Most of these issues occurred at the start of implementation and were resolved. Furthermore, it was often difficult to track the contacts as they were often 'too busy'. The most appropriate time to approach contacts was in the evening after work. Contacts were generally too busy to participate in the screening, probably as they already felt comforted by a negative result from the first screening. This was also considered by health staff as one reason that contacts were lost to follow up for the second screening. Additionally, many contacts could not found as wrong telephone number, inadequate or incorrect addresses were provided by the MDR-TB patients or some contacts moved to another place or changed their phone numbers. However, it was mentioned by some health staff that some MDR-TB patients did help to find the correct contact details.

It was also perceived there was a low awareness among contacts about TB and its transmission. Especially it was difficult to instruct for contacts with low level of education such as jobless people, or contacts belong to vulnerable groups such as drug users. Even information was provided about the risk of being infected with MDR-TB, some contacts refused to be involved in the study due to still feeling healthy and did not believe there was a need for a health check. Others were afraid of being considered as a TB patients if they would go to a TB health clinic.

Regarding high-risk places: generally restaurants did not agree or support to find contacts in their facilities. This was improved by the support from local authorities, involvement of local health facilities including staff working for food and hygiene programme to explain and persuade them to collaborate. It was then followed by local speaker to broadcast to call people who frequently visited the place during specific period to come for screening. The final issue was that 40% of the discussion participants found that social network analysis increased their workload. They regularly need to work after working hours or even in the weekend as health staff needed to spend extra time to go to the contact's home.

5.4 Discussion

We implemented social network analysis to detect more MDR-TB cases. Enrolling 99 MDR-TB cases and their contacts did not reveal any new MDR-TB case. Links between MDR-TB cases were found in two instances but did not lead to detection of new cases. One potential case was missed (resistance testing pending) as the patient's parents did not report to the district coordinators when the child had symptoms suggestive for TB and they also did not inform the hospital doctor about the risk of MDR-TB. As a result, the child was treated as a susceptible TB case for one month until death. Utilization of Xpert MTB/RIF to early diagnose TB in children, especially diagnose meningitis and MDR-TB in health facility outside the NTP is highly recommended. This approach would be implemented either by setting up Xpert machine in those health facilities or by establishment a specimen referral mechanism to the NTP for diagnosis.

Similar to TB patients in general, MDR-TB patients in this study were mainly distributed in working age category. The male-to-female ratio among MDR-TB patients in this study of 3.5:1 was similar to the ratio among TB cases notified in Vietnam (3:1), but lower than the ratio among TB cases detected in prevalence survey (5:1) [6]. The proportion MDR-TB with HIV positive was 4% which is less than that proportion (6%) in the whole country of Vietnam. However, the difference was not statistically significant[3](Table 5-2). The proportion of smear positive among MDR-TB in the study (76.8%) was higher than that proportion (72.9%) among pulmonary TB patients notified in Vietnam in 2014. This may be explained by the current case finding strategy for MDR-TB that mainly focuses on smear positive TB cases (refer to chapter 2 for more detail)[5]. The distribution of positivity grade among MDR-TB patients was similar to that proportion among TB cases detected in prevalence survey in Vietnam (unpublished data). While more than 50% of estimated MDR-TB patients among notified TB cases in Vietnam are new TB cases [3][19], the low proportion of MDR-TB among new cases in this study reflect the limitation of current policy of Vietnam to focus on screening for MDR-TB among previously treated cases (refer to chapter 2 in this thesis for more detail).

There was a drop out rate of 20.1% of contact at the first screening more than 60% at the second screening. The participation rate among household contacts was higher than that among contacts outside the household, and also female contacts had a higher participation rate as compared to males. Participation of contacts outside the household was challenging to realize as they often refused to participate as was also revealed during the discussion. Health education about TB and

MDR-TB among the general population, especially for transmission among contacts of MDR-TB should be more focused. Good communication skills of health staff is needed to improve the participant's participation. Better awareness and communication may also help to improve the participation of high-risk places to find potential contacts.

Health education for MDR-TB patients on MDR-TB transmission among contacts would raise patient's awareness of protecting their relatives and friends or colleagues from being infected. As result, they may become willing to provide contact's information correctly and adequately. In our study, it was better to trace contacts by going to their home for the first time to provide necessary information and obtain informed consent, rather than do by telephone. This approach would expect to decrease the proportion of contacts lost to follow up.

The fact that we found one potential pediatric case with TB meningitis who died reveals that a more awareness is needed among caregivers. In addition, there is a need to develop a system to record and manage the contacts of MDR-TB so that they would be well informed by the doctor to provide appropriate diagnostic testing and management. Regarding the preventive therapy for household contacts or close contacts of TB who are under five years old, the WHO recommends to treat them as presumed latent TB infection (LTBI) according to WHO's guidelines in case active TB is excluded[20]. However, at the moment, there is still controversy about whether preventive therapy should be provided to close contacts of MDR-TB and it is not recommended to routinely treat them with second-line anti-TB drugs [2]. Due to the poor outcomes of existing treatment regimen for active MDR-TB, an effective preventive therapy for LTBI of MDR-TB is considered as an important intervention to be explored, especially for children under five and HIV infected people[2].

Even though we did not find any new MDR-TB case through our social network analysis, this approach may still be worth consideration. Early detection and treatment of MDR-TB cases would prevent MDR-TB transmission from patients to others. Contacts of MDR-TB patients have high risk of getting TB infection from source patients; therefore, investigation of TB among contacts of a known or suspected cases of MDR-TB is crucial to reduce the ongoing transmission of drug-resistant strains of M. tuberculosis in a community[15][21]. Particularly family members of MDR-TB cases have been in close contacts with a highly infectious MDR-TB patient for a long duration due to long delays in MDR-TB treatment initiation. As such, the MDR-TB

prevalence among household contacts of MDR-TB patients is considered to be higher than TB prevalence among household contacts of drug-susceptible TB cases [2].

At this stage of the epidemic, when number of MDR-TB cases is still less than number of drug-susceptible TB patients, it is possible to carry out contact investigation. However, it requires the program to build capacity for staff and make staff available for this task.

Several studies have shown that active case finding among MDR-TB contacts face many challenges. MDR-TB patients may lost trust in TB treatment due to their experience in many failed TB treatment courses. Family member, learning from the experience, would likely to disagree to participate in screen and diagnosis program. They may even refuse to take MDR-TB treatment after being notified diagnosis result. While MDR-TB is curable, social barriers to MDR-TB treatment could be an important factor that needs to be taken into account when designing and implementing PMDT program[2].

Home visit by contact investigator is an effective method to interview and encourage household contacts to go under TB evaluation. By visiting index patients and their household contacts, the investigator would be able to observe, perform an environmental assessment, discuss and evaluate the risk of exposure, as well as to provide counseling to household contacts on symptoms suggestive of TB and when and where to seek for healthcare, and to provide social support [15].

The possible reason to explain why we found no new MDR-TB cases is that there could be a reduced fitness of MDR-TB, which is an important aspect to consider in the risk of transmission. There have been number of studies on the fitness of MDR-TB conducted in animal models [22][23] or in laboratory using competitive fitness assays [24]. As such, these studies did not take into account the potential clinical, environmental, and socio-economic factors that influence the possibility to cause a second case of TB from an index patient. A prospective cohort household follow-up study in South Lima and Callao, Peru suggests that during the first 3 years of exposure, MDR-TB patients are less likely to transmit the disease to their contacts than drug-susceptible tuberculosis patients[25]. This study implemented during 3 years following up household contacts, the TB incidence in household contacts of an MDR-TB index case is only about half that in household contacts of a drug-susceptible TB index case [25]. This finding

suggests a possible intervention to control MDR-TB. Additionally, in our study, the relative short time to follow up of 6 months may also explain why we did not detect any new case. It would take two-year follow up to find new cases due to the slow reactivation of latent tuberculosis infection after infection [26].

5.5 Conclusions

In this study of nearly 100 MDR-TB index cases we were not able to find new MDR-TB cases using social network analysis within a follow-up period of 6 months. More staff resources may be needed and better communication skills and community awareness, collaboration of non NTP health facilities is needed to enhance participation and improve MDR-TB case detection.

References

1. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008. World Health Organization Document. 2008;WHO/HTM/TB/2008.402:1-247.

2. World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland:World Health Organization Document. 2014;WHO/HTM/TB/2014.11:1-403.

3. World Health Organization. Global tuberculosis report 2014. Geneva, Switzerland: WHO; 2014. WHO/HTM/TB/2014.08

4. World Health Organization. The Global Plan to stop TB, 2011-2015, Transforming the Fight towards elimination of tuberculosis. Geneva, Switzerland: WHO, 2010

5. National Tuberculosis Control Program of Vietnam. Annual review meeting report of the National TB Control Programme of Vietnam, 2009-2014. Hanoi: National Tuberculosis Control Programme of Vietnam; Ref Type: Report.

6. Hoa NB, Sy DN, Nhung NV, Tiermersma EW, Borgdorff MW, Cobelens FGJ. National survey of tuberculosis prevalence in Viet Nam. Bull World Health Organ. 2010;88:273-80.

7. Thuy Hoang Thi Thanh, Sy Dinh Ngoc, Nhung Nguyen Viet, Hung Nguyen Van, Peter Horby, Frank GJ Cobelens and Heiman FL Wertheim. A household survey on screening practices of household contacts of smear positive tuberculosis patients in Vietnam. BMC Public Health 2014, 14:713.

8. National Tuberculosis Control Program of Vietnam. National Guidelines for Programmatic Management of Drug Resistance Tuberculosis. Hanoi: Ministry of Health; 2009: 1-142.

9. T. N. Buu, D. van Soolingen, M. N. T. Huyen, N. N. T. Lan, H. T. Quy, E. W. Tiemersma, M. W. Borgdorff, F. G. J. Cobelens. Tuberculosis acquired outside of households, rural Vietnam. Emerg. Infect. Dis. 2010; 16(9): 1466–8.

10. D. P. Drotman, J. E. Mcdade, C. Ben Beard, F. Collins, B. W. J. Mahy, N. Marano, M. I. Meltzer, J. A. Rankin, P. Rollin, A. Frey, T. Gryczan, R. Henry, A. Mather, C. Snarey, R. Tucker, A. Jordan, M. Marshall, S. Justice. Emerging infectious diseases, a Peer-Reviewed Journal Tracking and Analysing Disease Trends.Emerging Infectious Diseases. www.cdc.gov/eid .2006; 2(5): 719-882.

11. H. S. Schaaf, I. a Michaelis, M. Richardson, C. N. Booysen, R. P. Gie, R. Warren, P. D. van Helden, N. Beyers. Adult-to-child transmission of tuberculosis: household or community contact?. Int. J. Tuberc. Lung Dis.2003; 7(5): 426–31.

12. B. T. Mangura, E. C. Napolitano, R. J. McDonald, M. R. Passannante, L. B. Reichman. Mycobacterium tuberculosis Miniepidemic in a Church Gospel Choir.Chest. 1998; 113 (1): 234–7.

13. V. Thompson, B. T. Mangura, J. Ford, S. E. Valway, I. M. Onorato. Evaluation of Investigations Conducted of Tuberculosis.JAMA, 2002; 287(8): 991–5.

14. M. Peter M. Small, Philip C. Hopewell, Samir P. Sing, Antonio Paz, Julie Parsonnet, Delaney C. Ruston, Gisela F. Schecter, Charles L. Daley, Gary K.Schoolink. The New England Journal of Medicine. Massachusetts Medical Society,1994.

15. World Health Organization. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva, Switzerland: World Health Organization Document. 2012.WHO/HTM/TB/2012.9

16. V. J. Cook, S. J. Sun, J. Tapia, S. Q. Muth, D. F. Argüello, B. L. Lewis, R. B. Rothenberg, P. D. Mcelroy.Transmission Network Analysis in Tuberculosis Contact Investigations.JID. 2007;196:1517–27.

17. Stanley Wasserman, Katherine Faust. Social Network Analysis: Methods And Applications (Structural Analysis In The Social Sciences).. Cambridge University Press, 1994, p. 857.

18. V. J. Cook, L. Shah, M. Sc, E. Brodkin, S. Rempel, R. Moore, D. Ph, Y. Zhao, R. Holt, R. Varhol, I. Birol, M. Lem, M. K. Sharma, K. Elwood, S. J. M. Jones, F. S. L. Brinkman, R. C.

Brunham, and P. Tang.Whole-Genome Sequencing and Social- Network Analysis of a Tuberculosis Outbreak. N. Engl. J. Med. 2011; 364:730–9.

19. Nhung. N. V, Hoa.N. B, Sy.D. N, Hennig.C. M, Dean.A. S. The Fourth National Anti-Tuberculosis Drug Resistance Survey in Viet Nam. Int J tuber Lung dis. 2015; 19(6): 670–5

20. World Health Organization. Systematic screening for active tuberculosis. Principles and recommendations. World Health Organization Document. 2013;WHO/HTM/TB/2013.04:1-133.

21. M. Vree, N. T. Huong, B. D. Duong, D. N. Sy, L. N. Van, F. G. J. Cobelens, and M. W. Borgdorff. Mortality and failure among tuberculosis patients who did not complete treatment in Vietnam: a cohort study. BMC Public Health, 2007; 7(1): 134

22. Mitchison DA. Tubercle bacilli resistant to isoniazid; virulence and response to treatment with isoniazid in guinea-pigs. Br. Med. J. 1954; 1(1951): 128–30.

23. Ordway DJ, Sonnenberg MG, Donahue SA, Belisle JT, Orme IM. Drug-resistant strains of Mycobacte- rium tuberculosis exhibit a range of virulence for mice. Infect Immun. 1995; 63:741–743.

24. Gagneux S. Fitness cost of drug resistance in Mycobacterium tuberculosis. Clin Microbiol Infect. 2009; 15 (Suppl 1):66–68. doi: 10.1111/j.1469-0691.2008.02685.

25. L. Grandjean, R. H. Gilman, L. Martin, E. Soto, B. Castro, S. Lopez, J. Coronel, E. Castillo, V. Alarcon, V. Lopez, A. San Miguel, N. Quispe, L. Asencios, C. Dye, and D. a J. Moore. Transmission of Multidrug-Resistant and Drug-Susceptible Tuberculosis within Households: A Prospective Cohort Study. PLoS Med, 2015;12(6): e1001843.

26. Lillebaek T, Dirksen A, Baess I, Strunge B, Thomsen VØ, Andersen AB. Molecular evidence of endoge- nous reactivation of Mycobacterium tuberculosis after 33 years of latent infection. J Infect Dis. 2002; 185:401–404. doi: 10.1086/338342

Chapter 6. CONCLUSION

Nearly half a million multi-drug resistant tuberculosis (MDR-TB and XDR-TB) cases emerge globally every year as a result of under investment in TB control, poor management of supply and quality of second line TB drugs, improper treatment, and the transmission of disease in crowded settings [1]. The Global Stop TB strategy (2006-2015) has identified MDR-TB as one challenge and therefore the framework for drug resistance is organized around five comprehensive components of DOTS strategy including sustained political commitment, rational case finding strategy, appropriate treatment strategy, uninterrupted supply of quality-assured anti-tuberculosis drugs, standardized recording and reporting system [2].

Vietnam is 14th among 27 MDR-TB high burden countries with an estimated about 5,100 MDR-TB cases among notified TB cases per year [1]. Vietnam is also a country with confirmed XDR cases [3]. According to the result of the 4th National Drug resistance Survey (2005-2006), the proportion of MDR-TB in Vietnam is 4.0% among new cases and 23 % among previously treated cases [4]. Based on this result, the number of MDR-TB estimated among new cases and previously treated cases are 3,000 and 2,100, respectively. The majority of MDR-TB found among new cases in Viet Nam suggests an important source of transmission from MDR-TB to their contacts in the community.

This thesis provides an understanding of the current situation of MDR/XDR-TB in Vietnam and its control policies focusing on case finding strategy, targeting groups for MDR-TB screening. MDR-TB contacts, one of the high risk groups recommended by the WHO is also prioritized by studies to demonstrate the screening practice of household contacts, feasibility of contact investigation, and to identify challenges and solutions for a successful implementation of contact investigation among MDR-TB patients in Viet Nam. Below the key findings are presented.

MDR-TB control policies and practices

The first guideline initiated by WHO on Programmatic Management of Drug Resistant Tuberculosis was issued in 2006, following by three revision versions in 2008, 2011 and 2014[1][5][6]. The guideline is intended as a useful tool to guide public health professionals to effectively manage MDR-TB program in country. These documents cover guidance on

implementation of case-finding, treatment regimens, monitoring the response to treatment, and selecting models of care for drug resistance tuberculosis.

Since 2009, the programmatic management of drug resistant tuberculosis (PMDT) was piloted in Vietnam following the development of 2009 country MDR TB guideline. A year after WHO updated guideline disseminated, the country revised its guideline to be in line with WHO's recommendations and took into consideration the availability of capacity and resources. SOPs were developed following the issuance of national PMDT policies and a consultation with PMDT staff after a piloting period. The National TB Control Program has provided to provincial and district TB programme guidance and conducted training for their staff on policy and SOP implementation. PMDT has been rapidly scaled up in Viet Nam. Xpert MTB/RIF to test presumptive MDR-TB cases was introduced to the country one year after the 2011 WHO recommendation. However, lack of resources posed significant challenges for the NTP to implement their policy. Furthermore, often new guidelines or SOPs were not communicated well to the TB units and relevant staff resulting that staff do not which risk groups should be screened. Currently, the focus of MDR-TB screening is on certain high-risk groups rather than on new TB cases. There was delay in management of MDR-TB contacts, diagnosis of mono and poly resistant TB, as well as inadequate performance of second-line DST to diagnose XDR-TB. Expansion of risk groups for MDR-TB screening is key to increasing the detection of MDR-TB cases.

Detection of multidrug resistant tuberculosis

In 2013, among 5,065 estimated MDR-TB cases, only about 30 % was detected through the PMDT system. The possible reasons we identified were: (1) delay in fully rolling out PMDT policies and limited capacity of the system, mostly due to inadequate resources, (2) operational factors, and (3) neglecting high risk groups during MDR-TB screening.

The PMDT is more complex than for susceptible TB as it requires greater human, financial and technical resources. Viet Nam does not have a nation-wide PMDT coverage. Due to limited resources, Viet Nam PMDT policy gives priority to screen for MDR-TB among previously treated patients. Additionally, PDMT staff was often not well trained on the national policies

updated over time which have led to inadequate knowledge on policy implementation. There is a considerable delay in the development of SOPs, which took three years since implementing PMDT. Management of MDR-TB contacts and diagnosis of mono and poly resistant TB were delayed because of limited resources. Performance of second-line DST to diagnose XDR-TB has not been adequate.

Our study found that only one third of MDR-TB presumptive cases are screened by Xpert MTB/RIF in Vietnam. Although Xpert MTB/RIF testing was available in PMDT provinces, the system for transferring specimens for Xpert MTB/RIF testing generally was not adequate. For some periods, Xpert MTB/RIF test kits were stocked out. Distribution of Xpert MTB/RIF instruments has not yet based on workload of the health facilities.

The program has neglected to screen MDR-TB among new TB patients whose sputum had not converted after 2 or 3 months of treatment and TB patients with HIV. Those tested for MDR-TB were 340/3,224 (10.5%) of TB-HIV co-infected patients and 290/2,214 (13.1%) of patients who remained sputum smear-positive after 2 and 3 months of category I TB regimen. These groups account for the majority of presumptive MDR-TB cases.

In order to be able to detect more MDR-TB cases, Xpert MTB/RIF should be more easily accessible for those at risk of MDR-TB. Currently, Xpert machines are located in provincial levels and the instrument's capacity is considered to be sufficient. Stock outs of testing kits have resulted in not being able to test for a period of time. An appropriate test kit procurement-supply management should be in place. Also the lack of a well functioning specimen referral system to send samples from district to provincial level has contributed to the low numbers of suspects being actually tested. This can be improved by involving a shipping agency in sample referral with good safety standards. This approach is considered not too costly and feasible to implement in Vietnam. Another way of increasing the accessibility of MDR-TB presumptive to Xpert testing is to provide more Xpert machines further down to district level. This approach can address the problem of sample referral system; However, it requires a huge resource to procure, operate and maintain for a large quantity of machines and not considered as suitable for Vietnam.

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Enrollment for MDR-TB treatment

Among 5,100 estimated MDR-TB cases, only 18.7% was diagnosed and provided with second-line treatment. However, among those who were tested and detected with MDR-TB, it is encouraging that 95% of the patients were enrolled for treatment.

One of the challenges we found in the regions with relatively high MDR-TB testing coverage (such as, North-East, North-West, Northern Central and Southern Central Coast) is the low treatment enrollment rate (0% - 27.3%) was still found where there was relative high testing proportion. This is partly due to insufficient hospitalization capacity to provide service to patients in their locality. Our qualitative study suggested that many patients refused to be referred to another treatment centre in another province either due to distance from hometown or additional costs without getting health insurance reimbursement. There was also a poor link between public and private sectors in regards to MDR-TB treatment. Temporary MDR-TB drug stock-out due to procurement and distribution delay resulted in patients either not enrolled for treatment or a delay in treatment

Screening practices of household contacts of tuberculosis patients

For most of the Vietnamese population, the NTP strategy relies on "passive case finding". Passive case finding needs people to self-report with TB symptoms to primary health centers, and are then screened by sputum smear. Our survey on screening practices of household contacts of smear positive TB patients (chapter 3) showed that the proportion of household contacts of smear-positive tuberculosis patients screened for TB under the current passive screening approach of the Vietnam National TB program is very low compared with prevalence of TB among contacts in high burden countries, particularly for contacts under 5 years of age [7]. Of the 4,118 household contacts, 474 (11.5%) self-referred for TB screening, while this screening proportion was only 5.5% among contacts under 5 years old (16/293). Therefore, contact investigation should be conducted more actively and systematically, especially for close contacts of newly diagnosed TB patients, young children and contacts of drug-resistant TB. There is a need to establish a management system to follow up and screen for TB among close contacts of MDR-TB. Interestingly we found (chapter 4) that most TB cases from MDR household contacts are not MDR (they were screened within 1 year after MDR-TB patients diagnosed). This finding suggests that most MDR-TB is not easily transmitted and that contacts rather get TB from other

sources. We can not rule out that due to the relative short follow up time we may have missed MDR-TB cases.

Actively tracing of close contacts of MDR-TB cases

Although close contacts of MDR-TB patients are recommended by the NTP of Viet Nam to be screened for MDR-TB [8], there is not yet a clear mechanism for contact tracing in Viet Nam. Household contacts are classified as a risk group but currently undergo a passive case finding approach. Data from our prevalence survey conducted in 2006-2007 showed that this existing passive case finding approach can only detect about 60% of patients, leading to the recommendation to conduct an active case finding approach in risk groups [9]. Our study on household contact investigation also shows a low proportion of contacts screened with a passive approach (Chapter 3) [10].

Traditional contact investigation of only household members is not sufficient to identify the transmission of MDR-TB and additional approaches are needed. Additional information should be collected from MDR-TB patients regarding their contacts outside household and their residence and other sites where transmission might have occurred [11]. Social network Analysis (SNA) is a more comprehensive approach than traditional contact tracing which includes a set of persons (nodes) and the connections (ties) among them for analysis of structure of disease transmission[12]. Our study of SNA of nearly 100 MDR-TB index cases were not able to find new MDR-TB cases among 417 close contacts within a follow-up period of 6 months. The fact we found no new MDR-TB cases may be explained by reduced fitness of MDR-TB[13], high drop out proportion and the short follow up time of our study of 6 months. Fitness of an organism refers to its ability to survive, reproduce and transmit from one host to the other. It is assumed that resistance can affect the essential function of an organism and cause a metabolic cost resulting in fitness cost. In this case, the resistant strain may be less fit than its sensitive ancestor organism [14][15]. However, fitness of some strains were not reduced after becoming resistant[14][16]. This may be explained by adaptive mechanisms making the resistant variant maintain its fitness [17]. Bacterial fitness varies among members of species and depends on numerous factors. Some fitness characteristics of mycobacterium tuberculosis are measurable in the laboratory such as the culture growth rates [18][19], infectivity in animal experiments [20][21]. The ability to be disseminated can be ascertained by the prevalence of these strains in

the community. Although fitness cost is likely a result of MDR-TB [13][22], our study has no data on the strain characteristics of recruited MDR-TB patients, it is impossible to measure its fitness compared to susceptible isolates and warrants further investigations.

Even though we did not find any new MDR-TB cases through our social network analysis, this approach may still be worth consideration. MDR-TB detected and treated early may prevent further transmission. Our study also revealed many difficulties to contact investigation. MDR-TB patients' were often hesitant on being interviewed to give the information regarding their contacts. Participation of contacts outside the household was challenging to realize as they often refused to participate. Health education about TB and MDR-TB among the general population, especially for transmission among contacts of MDR-TB should be more focused. Good communication skills of health staff is needed to improve the participant's participation.

Recommendations
Based on this thesis we recommend the following:

- Standardize and decentralize training on PMDT;
- Provide NTP staff with updated information on policy change and ensure this is received;
- Expand capacity on MDR-TB treatment; this should also increase MDR-TB case finding;
- Expand ambulatory care of MDR-TB treatment;
- Expand risk group for MDR-TB screening;
- Strengthen case findings of MDR-TB by:
    o Provide information, educate close contacts of MDR-TB patients, with special attention to children;
    o Conducting more research on how active contact investigations should be done to have the best yield.
- Allocate more resources to MDR-TB control, particularly well-trained staff.

References

1. World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland:World Health Organization Document. 2014;WHO/HTM/TB/2014.11:1-403..

2. World Health Organization. The Global Plan to stop TB, 2011-2015, Transforming the Fight towards elimination of tuberculosis. Geneva, Switzerland: WHO, 2010

3. World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB). 2010 Global report on surveillance and response. Geneva, Switzerland:World Health Organization Document. 2010;WHO/HTM/TB/2010.3.

4. Nhung. N. V, Hoa.N. B, Sy.D. N, Hennig.C. M, Dean.A. S. The Fourth National Anti-Tuberculosis Drug Resistance Survey in Viet Nam. Int J tuber Lung dis. 2015; 19(6): 670–5

5. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008. World Health Organization Document. 2008;WHO/HTM/TB/2008.402:1-247.

6. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. 2011 update. World Health Organization Document. 2011;WHO/HTM/TB/2011.6:1-33.

7. Rieder H L. Contacts of tuberculosis patients in high-incidence countries. Int J Tuberc Lung Dis 2003;7(suppl 3):S333-S336

8. National Tuberculosis Control Program of Vietnam: National Guidelines for Programmatic Management of Drug Resistance Tuberculosis. Hanoi: Ministry of Health; 2009: 1-142.

9. Hoa NB, Sy DN, Nhung NV, Tiermersma EW, Borgdorff MW, Cobelens FGJ. National survey of tuberculosis prevalence in Viet Nam. Bull World Health Organ. 2010;88:273-80.

10. Thuy Hoang Thi Thanh, Sy Dinh Ngoc, Nhung Nguyen Viet, Hung Nguyen Van, Peter Horby, Frank GJ Cobelens and Heiman FL Wertheim. A household survey on screening practices of household contacts of smear positive tuberculosis patients in Vietnam. BMC Public Health 2014, 14:713

11. World Health Organization. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva, Switzerland: World Health Organization Document. 2012.WHO/HTM/TB/2012.9

12. V. J. Cook, L. Shah, M. Sc, E. Brodkin, S. Rempel, R. Moore, D. Ph, Y. Zhao, R. Holt, R. Varhol, I. Birol, M. Lem, M. K. Sharma, K. Elwood, S. J. M. Jones, F. S. L. Brinkman, R. C. Brunham, and P. Tang.Whole-Genome Sequencing and Social- Network Analysis of a Tuberculosis Outbreak. N. Engl. J. Med. 2011; 364:730–9.

13. Gagneux S. Fitness cost of drug resistance in Mycobacterium tuberculosis. Clin Microbiol Infect. 2009; 15 (Suppl 1):66–68. doi: 10.1111/j.1469-0691.2008.02685.

14. Gillespie, S. H, McHugh, T. D. The biological cost of antimicrobial resistance. Trends Microbiol., 1997; 5(9): 337-39.

15. R. J. Shorten. The molecular epidemiology of Mycobacterium tuberculosis in north London. 2011. http://discovery.ucl.ac.uk/1310448/

16. Bjorkman, J., Samuelsson, P., Andersson, D. I., Hughes, D. Novel ribosomal mutations affecting translational accuracy, antibiotic resistance and virulence of Salmonella typhimurium. Mol.Microbiol; 1999. 31 (1): 53-58.

17. Andersson, D. I. Levin, B. R. The biological cost of antibiotic resistance. Curr.Opin.Microbiol;1999; 2 (5): 489-93.

18. Billington, O. J., McHugh, T. D., Gillespie, S. H. Physiological cost of rifampin resistance induced in vitro in Mycobacterium tuberculosis. Antimicrobial Agents and Chemotherapy; 1999; 43 (8):1866-69.

19. Gagneux, S., Long, C. D., Small, P. M., Van, T., Schoolnik, G. K., Bohannan, B. J. The competitive cost of antibiotic resistance in Mycobacterium tuberculosis. Science, 2006; 312

(5782):1944-46.

20. Heym, B., Stavropoulos, E., Honore, N., Domenech, P., Saint-Joanis, B., Wilson, T. M., Collins, D. M., Colston, M. J., Cole, S. T. Effects of overexpression of the alkyl hydroperoxide reductase AhpC on the virulence and isoniazid resistance of Mycobacterium tuberculosis. Infect.Immun. 1997. 65 (4): 1395-1401.

21. Li, Z., Kelley, C., Collins, F., Rouse, D., Morris, S. Expression of katG in Mycobacterium tuberculosis is associated with its growth and persistence in mice and guinea pigs. J.Infect.Dis., 1998; 177 (4): 1030-35.

22. Grandjean, R. H. Gilman, L. Martin, E. Soto, B. Castro, S. Lopez, J. Coronel, E. Castillo, V. Alarcon, V. Lopez, A. San Miguel, N. Quispe, L. Asencios, C. Dye, and D. a J. Moore. Transmission of Multidrug-Resistant and Drug-Susceptible Tuberculosis within Households: A Prospective Cohort Study. PLoS Med, 2015;12(6): e1001843.

Appendix 1. DEFINITION AND INTERVIEW GUIDE

Definition of presumptive MDR-TB case:

Presumptive MDR-TB cases are individuals who are considered to be at high risk for MDR-TB. Various MDR-TB risk groups are defined by the National Tuberculosis Programme. In 2012, with the introduction of the Xpert MTB/RIF for MDR-TB diagnosis, the case finding strategy was extensively discussed by the central PMDT task force. It was decided that MDR-TB risk groups should include: retreatment cases (including relapse), treatment failure, treatment after default, HIV positive TB patients, and household contacts of MDR-TB cases, individuals who have a history of using TB drugs for more than 1 month. The following groups are considered as MDR-TB presumptive case:

- Treatment after failure of Category I (for new TB cases) and/or Category II (for retreatment cases). Failure is defined as sputum smear positive at five months or later during treatment.

- Relapse of Category I and/or Category II. Relapse is defined as a patient whose most recent treatment outcome was "cured" or "treatment completed", and who is subsequently diagnosed with bacteriologically positive TB by sputum smear microscopy or culture individuals that shares the same house with index TB cases including anyone staying in the house for at least 3 months leading up to the time of diagnosis of the index cases

- Treatment after default of Category I and/or Category II. Default is defined as a patient who returns to treatment, bacteriologically positive by sputum smear microscopy or culture, following interruption of treatment for two or more consecutive months.

- Other TB patients, including TB patients who were previously treated for TB in the private sector with unknown outcome, and/or patients who were diagnosed as smear negative in previous TB treatment course, but are currently smear positive.

- TB patients whose sputum did not convert after 2 and 3 months of Category I regimen.

- TB patients whose sputum did not convert after 3 months of Category II regimen.

- Symptomatic individual who have contacts with a confirmed MDR-TB

- A new TB patient (either smear positive or negative) who are infected with HIV

o TB suspects with history of using TB drugs for more than 1 month (not diagnosed as TB neither by the NTP nor by private sector and use any TB drugs for diseases other than TB*)* .

Estimation of presumptive MDR-TB cases for special risk groups who are not notified to the NTP:

o The number of symptomatic contacts: This estimation is applied for household contacts only. Currently, there is no clear mechanism for contact management in Vietnam and household contacts undergo a passive case finding approach; they are advised to seek help if symptomatic. It is estimated that one MDR-TB patients will have 4 household contacts on average [8]. Percentage of TB suspects among contacts (symptomatic contacts) is estimated at about 10% in the first year based on results from studies which showed about 5-12 % of suspects need to be examined to detect one TB case [9], and the TB prevalence among contacts at baseline was 734/100.000, incidence rate among contacts in the first year of exposure is about 180/100.000[8] .

o TB suspects with a history of using TB drugs for more than 1 month : Currently, there is no data on the number of individuals who have previously taken TB drugs for more than one month to treat disease other than TB. However, this number is expected to be limited and estimated to be ~2% of retreatment cases.   .

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Calculation for the estimate number of MDR-TB cases to be detected per instrument per year

Ser. No	Region	Estimated number of MDR-TB	Number of Gene Xpert	Number of MDR-TB/ machine/year
1	Red river delta	627	9	70
2	North-East	189	2	95
3	North-West	9	1	9
4	Northern Central	338	1	338
5	Southern Central coast	304	3	101
6	Central highland	21	0	NA
7	South East	1,408	11	128
8	Mekong delta	1,086	5	217
	Total	3,982	32	124

Calculation of testing capacity for Xpert MTB/RIF instrument:

Calculation is made based on the following assumptions:

- One instrument has 4 modules, and 1 module can perform one test.
- A test requires 2 hours for testing by Xpert MTB/RIF.
- The machine can only be operated during working hours, which is about 7 working hours per 24 hours. It will not be operated in the weekend.
- Therefore there can be a maximum 3 testing rounds per day. With 22 days per month the annual testing capacity is thus 3,168 tests.

Assumed that the proportion of rifampicin resistance among tested MDR-TB presumptive cases is 17.6% (as shown in this study), it is estimated that there will be approximately 557 rifampicin resistance TB patients among 3,168 MDR-TB presumptive cases tested.

PMDT provinces participated in focus group discussion and in-depth interview

Name of PMDT province by region	Number of provinces	Focus group discussion	In-depth interview
Red River Delta region (Ha Noi, Hai Phong, Vinh Phuc, Hai Duong, Hung Yen, Nam Dinh, Thai Binh	7	Group 1	1 province (Hai Duong)
North-East region (Thai Nguyen, Quang Ninh, Bac Giang)	3	Group 2	1 province (Quang Ninh)
North-West regions (Dien Bien).	1		
Northern Central region (Thanh Hoa, Nghe An, Thua Thien Hue: 3 provinces)	3		
Southern Central Coast (Da Nang, Quang Nam, Binh Dinh, Khanh Hoa)	4	Group 3	2 provinces (Da Nang, Quang Nam)
Central Highland (Lam Dong)	1		
South-east (Ba ria Vung tau, Binh Thuan, Dong Nai, Ninh Thuan, Tay Ninh, HCMC)	6	Group 4	4 provinces (Ba ria Vung Tau, Binh Thuan, Ninh Thuan, HCMC)
Mekong River delta regions (An Giang, Bac Lieu, Ben Tre, Ca Mau, Can Tho, Dong Thap, Kien Giang, Long An, Soc Trang, Tien Giang)	10	Group 5	No
Total	35	5	4

INTERVIEW GUIDE

1. Does your TB unit belong to a hospital or health center?
2. If your TB unit belongs to health center, does the provincial TB program provide training for district hospital staff? If not, do you know why not?
3. Can you name the MDR-TB risk groups (as many as you can)?
4. Can you tell us why do you think they are at high risk for MDR-TB infection? How do you define MDR-TB presumptives by risk group in your setting? What did you do when a MDR-TB presumptive defined? Probe for the following steps:

   (ii) Referring presumptive cases for diagnosis

   (iii) Drug resistance testing,

   (iv) Obtaining informed consent from patients for treatment, and

   (v) Enrollment of diagnosed MDR-TB patients to treatment.

5. Can you describe the role of your unit in PMDT implementation, probe for the following steps:

   (i) Identification of presumptive MDR-TB cases (individuals considered at high risk for MDR- TB) according to case definitions

   (ii) Referring presumptive cases for diagnosis

   (iii) Drug resistance testing

   (iv) Obtaining informed consent from patients for treatment, and

   (v) Enrollment of diagnosed MDR-TB patients to treatment.

6. What are difficulties and challenges encountered for PMDT implementation in your setting? Probe for the following steps:

   (i) Identification of presumptive MDR-TB cases (individuals considered at high risk for MDR- TB) according to case definitions

   (ii) Referring presumptive cases for diagnosis

   (iii) Drug resistance testing

   (iv) Obtaining informed consent from patients for treatment, and

   (v) Enrollment of diagnosed MDR-TB patients to treatment.

7. How are policy changes informed to you (by whom and by which way?) Did you get these changes informed adequately? If not, what obstacles to get the policy changes informed?

8. What training topics provided? What was the quality of the training? What kind of training material was used? Do you think the trainings were adequate (fulfilled your needs) or not? If not, Why?

Appendix 2. OPERATIONAL DEFINITIONS

MDR-TB presumptive: In this study, the MDR-TB presumptive referred to (i) any MDR-TB contact (adults and adolescents) with clinical symptom suggested for TB orabnormal findings consistent with TB on the Chest X-ray (CXR). The most common symptom is a productive cough for more than 2 weeks, which may be accompanied by other symptoms(shortness of breath, chest pains, haemoptysis) and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats, and fatigue), (ii) any children who was MDR-TB contact with one of the following: poor weight gain (failure to thrive), 2 weeks of fever or cough, abnormal findings consistent with TB on CXR, recent poor consciousness, enlarged cervical lymphadenopathy iii) any TB patients who were on current first line anti TB treatment.

Confirmed tuberculosis. In this investigation, a case of tuberculosis includes (i) sputum smear examination positive for acid-fast bacilli (AFB), (ii)any specimen positive for Mycobacterium tuberculosis complex by either culture or molecular methods.

Multidrug-resistant tuberculosis (MDR-TB case): defined as TB caused by strains of *Mycobacterium tuberculosis* that are resistant to at least isoniazid and rifampicin. In this study, patients who are tested by Gene-X-pert and are positive for rifampicin resistant TB will be also classified as MDR-TB (because more than 96% of rifampicin resistance in Vietnam is also resistant to isoniazid).

Active case finding or active screening: Active effort by health workers to find TB cases in the community (among identified eligible contacts in this study) who do not seek consultations in health facilities.

Passive case finding: Finding a case of tuberculosis from symptomatic patients who present themselves at the health facilities.

Index MDR-TB case: the rifampicine resistant or MDR-TB patient who was diagnosed and enrolled to treatment by routine system.

Household: includes all the persons who occupy a housing unit as their usual place of residence. A housing unit is a house, an apartment, a group of rooms, or a single room that is occupied by a single family, one person living alone, two or more families living together, or any other persons who share living arrangements.

MDR-TB contact: anyone who spend time with MDR-TB patients either in household or in other in-house environment.

Household contact: all household members of the MDR-TB patients, including children who should have been in the household at least 4 hours a day, for at least 14 days, or a cumulative total average exposure of at least 8 hours per week for at least 8 weeks during 3 months leading up to the time of TB diagnosis.

Close contact: any individual apart from household members who also have frequent and prolonged contact with the MDR-TB patients in in-house environment during 3 months leading up to the time of TB diagnosis. This may include friends, frequent visitors, work colleague, school/class mate, team club member who spend at least 4 hours a day, for at least 14 days, or a cumulative total average exposure of at least 8 hours per week for at least 8 weeks together with the patient in in-house environment.

Mutual contact: a contact that is named by at least 2 confirmed MDR-TB patients.

Mutual place: a place that is named by at least 2 confirmed MDR-TB patients.

High risk place: The in-house condition place where the MDR-TB index case spend an average of at spend at least 4 hours a day for at least 14 days, or a cumulative total average exposure of at least 8 hours per week for at least 8 weeks in3 months prior MDR-TB diagnosis.

Eligible place: includes mutual places and high risk places.

Eligible contact: Includes (i) household contacts, (ii) close contacts, (iii) mutual contacts who have contact during 3 months leading up to the time of TB diagnosis for at least 1 patient (iv) people who frequently visited the eligible places during 3 months leading up to MDR-TB diagnosis and found to be TB suspects by primary interview. These contacts are eligible for both active screening and passive case detection.

Categories of patients:

- New: Patients who received no TB drugs or used them for less than one month
- Non-converters of first line anti TB drugs for new cases: Patients whose sputum was not converted after 2 months of first line anti TB drugs treatment among new TB cases
- Non-converters of first line anti TB drugs for retreatment cases: Patients whose sputum was not converted after 2 and/or 3 months of first line anti TB drugs treatment among retreatment TB cases
- Previously treated cases: Includes relapsed cases, treatment failed cases, treatment after loss to follow-up cases
- Others: includes TB patients who were previously treated for TB in the private sector with unknown outcome, and/or patients who were diagnosed as smear negative in previous TB treatment course, but are currently smear positive.