# Tuberculosis control in Vietnam : does DOTS do it?

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**Nguyen Thien Huong**

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**Table of contents**

# Chapter 1

# General Introduction

## GLOBAL EPIDEMIOLOGY OF TUBERCULOSIS: BURDEN OF DISEASE

The World Health Organization (WHO) declared tuberculosis (TB) a global public health emergency in 1993 [1]. About one third of the world's population is infected with *Mycobacterium tuberculosis* (*M. tuberculosis*). It is estimated that, in 2005, there were 8.8 millions new cases of tuberculosis, of which 3.9 million were smear-positive and 11% were in adults infected with the human immunodeficiency virus (HIV) ), as well as 1.6 million TB deaths worldwide. More than 80% of all TB patients in 2005 lived in Asia and Sub-Saharan Africa [2].

In 2005, the TB incidence rate was stable or in decline in all six WHO Regions. However, the total number of new TB cases was still rising slowly [2]. Today, TB is still one of the world's leading causes of death and of the global burden of disease. It is estimated that between 2002 and 2020, approximately 1,000 million people will be newly infected, over 150 million will become sick and 36 million will die of TB if proper control measures are not instituted [3].

Poverty, HIV and multidrug-resistant tuberculosis (MDR-TB) are key factors driving the TB epidemic.

TB is principally a disease of poverty, 95% of TB all cases and 98% of deaths from tuberculosis are in developing countries [4]. Vulnerability to active TB has been strongly correlated with the conditions and consequences of poverty, such as malnutrition, inadequate and overcrowded housing, and unsanitary working conditions [5-12]. As 75% of TB cases in developing countries are people in their most economically productive age groups (15-50 years) [13], a vicious circle ensues in which, TB itself is a cause of poverty.

The greatest emerging threat to TB control arises from the HIV pandemic. During 2005 alone, an estimated 2.8 million persons died from AIDS, 4.1 million were newly infected with HIV, and 36.6 million were living with HIV [14].

HIV may alter the epidemiology of tuberculosis in several ways [15]. HIV promotes progression to active TB both in people with recently acquired (16) and with latent [4,17] *M.tuberculosis* infection. HIV infection is the most powerful risk factor recognized in the progression to active disease from pre-existing infection with *M. tuberculosis* [18].

HIV increases not only the risk but also the rate of progression of recent or latent *M. tuberculosis* infection to disease [19-21]. HIV also increases the risk of recurrent TB after successful TB treatment [22].

Persons co-infected with HIV and *M. tuberculosis* have a five to ten-fold increased risk of developing active TB compared to those infected with *M. tuberculosis* alone [17]. Increasing tuberculosis incidence in people living with HIV/AIDS (PLHA) poses an increased risk of TB transmission to the general community, whether or not HIV-infected [23]. Over time, the greater risk and propensity to develop active TB among HIV-infected

persons, particularly in countries of high TB burden, can lead to rapid increases in TB incidence and prevalence.

TB, although preventable and treatable, is one of the most common causes of morbidity and mortality among PLHA worldwide [24-30].

By the end of 2000, of the 11 million people worldwide were co-infected with *M. tuberculosis* and HIV, with 71% of those co-infected living in sub-Saharan Africa and 22% living in South-East Asia [31].

HIV fuels the TB epidemic where the population infected with *M. tuberculosis* overlaps with the population infected with HIV. In many countries of Africa and Southeast Asia, infection with HIV resulted in a rapid increase of TB morbidity and mortality [32-34]. HIV prevalence in tuberculosis patients is less than 1% in the Western Pacific region but 38% in Africa [24]. In countries with the highest HIV prevalence, more than 75% of cases of TB are HIV-associated [2].

In addition to HIV-associated TB, multidrug resistant tuberculosis (MDR-TB) is an increasing threat. Data from the global reports on resistance to anti-TB drugs have shown that drug resistance is present worldwide [37-42] with an estimated 424,203 new cases of multidrug resistance TB (MDR-TB) - which are resistant to at least the two most powerful first-line drugs (isoniazid and rifampicin) – in 2004 [40,41]. Most MDR-TB cases are found in three countries – China, India and the Russian Federation – accounting for 62% of the estimated global burden [41]. The prevalence of resistance among previously untreated patients reflects programme performance over a long period of time, and indicates the level of transmission within the community [40]. Outbreaks of multidrug-resistant tuberculosis have been reported from both industrialized and developing countries in patients with HIV infection [37-40]. HIV itself does not cause nor promote the development of multidrug resistance, but it fuels its spread by accelerating the progression from infection to disease [43]. The cost of detecting and treating of MDR-TB was 10- to 100-fold higher than susceptible TB patients. Even when second line drugs are available, the course of treatment takes much longer (18-24 months), its efficacy is lower and adverse reaction rates are higher [44].

In September 2006, the WHO has expressed concern over the emergence of virulent drug-resistant strains of tuberculosis: extensively drug-resistant tuberculosis (XDR-TB) which accounted for on average 10% of the detected MDR-TB case [45]. XDR-TB is TB that is resistant to at least isoniazid and rifampin among the first-line anti-TB drugs (which is the definition of MDR-TB), and in addition to that to any fluoroquinolone and to at least one second-line injectable drug (amikacin, capreomycin or kanamycin) [46]. XDR-TB makes treatment nearly impossible with currently available anti-TB drugs and has extremely high mortality rates. Data from South Africa (2006) showed that out of 1,539 TB cases diagnosed between January 2005 and March 2006, 542 were culture positive, 221 were MDR and 53 XDR cases. Out of 53 “possible” XDR patients, 52 (98%) died with a median survival from sputum collection of 16 days (range 2-210 days) [47-50].

Drug-resistant tuberculosis is a man-made problem. The development of drug resistance is a consequence of inadequate TB control, poor patient or clinician adherence to standard TB treatment regiments, poor quality drugs or inadequate drug supplies [51-56].

## NATURAL HISTORY OF TUBERCULOSIS

Tuberculosis (TB) is a bacterial disease caused by *M. tuberculosis* and spread by airborne droplet nuclei, which are particles of 1–5μm in diameter that contain *M. tuberculosis*, when people with pulmonary TB cough, sneeze, sing or talk [57-59].

TB principally affects the lung. Extrapulmonary TB accounts for about 20% of disease in HIV-seronegative people but is more common in HIV-seropositive individuals [60]. Patients with pulmonary TB whose sputum is smear-positive for *M. tuberculosis* are the main source of infection [61-65].

The risk of becoming infected with tubercle bacilli depends on the incidence of infectious cases in the community, the duration of their infectiousness, and the number and nature of interactions between a case and a susceptible contact per unit time of infectiousness [66,67]. Data from the pre-chemotherapy era showed that one infectious person infected approximately 20 persons during the average 2-year period that the patient remained infectious [66].

Infected persons can probably develop TB at any time depending on time since infection, age and host immunity. People with latent TB infection have about 10%-20% risk of developing active TB during their lives [67-70]. The risk is highest in the first two years after infection [71].

The risk of developing active TB is greatly increased by HIV co-infection [72,73]. The annual risk of developing TB in PLHA who are co-infected with *M. tuberculosis* can be exceeded 10%. This risk increases with increasing immunosuppression [74-76].

Without treatment, by the end of 5 years 50% of PTB patients have died, 25% are healthy (self cured) and 25% have chronic infectious TB [77]. In a poorly implemented tuberculosis programme, as many as 30% of patients with smear-positive tuberculosis die [78]. However, under the WHO Stop TB Strategy, the fatality rates throughout the world are less than 5% [2,79]. Adequate chemotherapy not only prevents tuberculosis patients from dying, but also cures them and prevents them from becoming chronic cases [80], as well as reduces the risk of drug resistance [81].

However, much higher death rates were reported for patients treated for HIV associated TB [82-93]. Overall, the case fatality rate of HIV-infected TB cases was 40% across all countries [24]. In sub-Saharan Africa, approximately 30% of HIV-infected, smear-positive tuberculosis patients died within 12 months of starting treatment, and about 25% of those

who completed treatment died during the subsequent 12 months in the absence of antiretroviral treatment or prophylactic treatment of opportunistic infections [17].

## TUBERCULOSIS CONTROL

The ultimate goal of tuberculosis control is the elimination of TB from the population by reducing the transmission of *M. tuberculosis* infection, resulting in the eventual disappearance of the disease [94]. The key to control TB is rapid detection and cure of infectious cases by TB control programmes. This depends on the timely diagnosis and treatment of the patients with smear-positive pulmonary tuberculosis; the cure of such patients is currently the only form of primary prevention of the disease and therefore diagnosis and treatment at present form the cornerstone of preventive activities for this disease [94]. In addition, vaccination with Bacille Calmette-Guérin (BCG) will supplement tuberculosis control efforts, particularly in high-burden countries, mainly by reducing disability and death in young children [94-97]. However, the protective efficacy of BCG against adult pulmonary TB is limited and its impact on TB transmission is probably minimal [98,99].

The modern strategy of TB treatment is based on standardized short-course chemotherapy (SCC) regimens, applied under proper case management conditions [100]. Standardized treatment is a component of the TB control policy package [101].

The global targets for tuberculosis control are to cure at least 85% of sputum smear-positive patients under treatment and to detect at least 70% of the estimated new sputum smear-positive cases. WHO adopted these targets and began to promote this strategy in 1991 [102-105]. In 1994 WHO produced a Framework for Effective Tuberculosis Control [106] that clearly described the main components of what later became known as the DOTS Strategy. The Framework was revised and expanded in 2002 [107,108], and recently revised as the Stop TB Strategy [109,110].

The Millennium Development Goals include the WHO tuberculosis control targets and aim to decrease the prevalence and death rates of tuberculosis by 50% by 2015 compared with 1990 [111,112].

The DOTS Strategy comprises five elements considered essential for global TB control [106]:

- Political commitment to long-term TB control activities;
- Case detection using sputum smear microscopy among persons seeking care for prolonged cough;
- Standardized short-course chemotherapy of 6 to 8 months for at least all sputum smear-positive cases, with directly observed treatment for at least the initial 2 months;
- Regular, uninterrupted supply of all essential anti-TB drug;

- A standardized recording and reporting system that allows assessment of treatment results for individual patients and of the TB control programme performance overall.

In a number of countries, the DOTS Strategy has been shown to be effective in reducing mortality [113,114] prevalence [115] and incidence [113], at least in the absence of HIV.

The World Bank recognizes that the DOTS Strategy is one of the most cost-effective of all health interventions and recommends that effective TB treatment should be a part of the essential clinical services package available in primary health care. DOTS produces significant savings for governments and communities [116-120]. For each dollar invested in DOTS, the expected return in increased economic output is more than $3.50 [116]. A study conducted in Thailand even suggested that for every US$ 1 invested by the government in tuberculosis control, the community gains by US$ 50 over a 20-year period [121].

A total of 187 countries and territories were implementing the DOTS Strategy in 2005. By 2005, 89% of the world's population lived in areas where DOTS had been implemented by public health services; the global treatment success rate among new smear-positive TB cases had reached 84%; and 60% of new smear-positive cases were estimated to be diagnosed by DOTS programmes and put on short-course chemotherapy [2].

However, current rates of progress are insufficient to achieve the targets of halving TB mortality and prevalence by 2015 [122,123]. Globally, the total number of new TB cases was still rising. In areas like the former Soviet Union and Sub-Saharan Africa, incidence is increasing rather than declining [2,24,25]. Much of the increase in global TB incidence seen since 1980 is attributable to the spread of HIV compounded by an insufficient health infrastructure in Africa despite maintaining reasonable treatment completion rate [24,25,34,122-124] whereas the economic decline, poor tuberculosis control and substandard health services since 1991 in Eastern Europe have contributed to a major increase in the incidence and prevalence of TB including MDR-TB [39].

The current Global Stop TB Strategy has been built on the DOTS Strategy and has an expanded scope to address remaining constraints and challenges to TB control [108,109]. The Stop TB Strategy has 6 principal components:

- Pursue high-quality DOTS expansion and enhancement
- Address TB/HIV, MDR-TB and other challenges
- Contribute to health system strengthening
- Engage all care-providers
- Empower people with TB, and communities
- Enable and promote research

This strategy is believed to be critical to achievement of the MDG and related Stop TB Partnership targets for TB control [109,110].

## METHODS FOR MEASURING THE IMPACT OF TUBERCULOSIS CONTROL

The impact of TB control efforts on the epidemic can be measured by the trends of morbidity (case notification rate (CNR), incidence, prevalence), mortality, and transmission [67]. Morbidity data is most direct, whereas trend in mortality is more a proxy for trend in morbidity.

Trends in incidence are difficult to measure because not all TB patients are diagnosed, and the proportion of incident TB cases that is detected (the case detection rate) is often unknown. Moreover, operational factors affect notification of detected cases. At a constant level of case detection and notification of detected cases, the trend of notification is a valid proxy for the trend in incidence.

Trends in prevalence of TB in the community can be detected directly through periodic TB prevalence surveys. However, such surveys are not regularly conducted since they are expensive and complex.

Trends in TB mortality can be monitored by death certification trends over several years. However, these data may not always be available, or may often be imprecise so that changes are seen only after several years. The most evident impact on mortality is the trend of deaths in patients under treatment.

Trends in TB transmission can be measured by assessing the trend of the annual risk of TB infection (ARTI) [125]. The ARTI is defined as the average risk for a person to be infected or re-infected with *M. tuberculosis* over the period of one year [66,126]. Trends in ARTI are obtained from surveys of tuberculin skin testing among children that are repeated over the time [127,128].

The prevalence of drug resistance indicates the negative impact of poor quality treatment and is used as a complementary indicator. The prevalence of MDR among new cases reflects the level of sustained transmission of MDR-TB and thereby provides an indicator of quality of treatment that is independent of reported treatment outcomes. A high rate of primary multidrug-resistant tuberculosis interferes with the achievement of high cure rates through an increase of failures (drug resistance) and of case-fatality.

## STUDY PROJECT

There is global consensus that the DOTS Strategy is the key to successful TB control. At the core of this strategy is early detection and effective treatment, by supervised short-course chemotherapy, of sputum-smear positive (i.e. highly infectious) cases of pulmonary TB [129].

The rationale is that it will decrease the pool of infectious TB in the population as a result, fewer people get infected and the epidemic will gradually die out. Epidemiological modeling has demonstrated that achieving the targets of 85% cure rate and 70% case

detection will result in a significant decline in tuberculosis incidence [66,130,131]. Achievement of these targets for case detection and cure is expected to reduce the annual TB incidence rate by 8-12% per year and an even faster reduction in mortality of 9–13% per year, in the absence of HIV co-infection. At 7% annual decline, incidence would be halved in 10 year [130,132].

The question however is whether a DOTS programme that reaches these targets sufficient to control the TB epidemic? (e.g. Does DOTS do it ?)

These theoretical figures from modeling are supported by more direct evidence from Europe and developing countries. Tuberculosis declined rapidly in Europe over the last century. The fall in incidence of infection accelerated from 4–5% to 12–13% per year following the introduction of effective treatment [66,67]. Rapid declines in tuberculosis incidence at 7-10% per year have been shown in developing countries applying the DOTS Strategy such as Peru and China.

In Peru, where the DOTS Strategy was introduced in 1990, the WHO targets were reached by 1995 and have been maintained since. The estimated case detection rate was more than 90% in 1999 and 90% of TB cases were successfully treated. Notification rates of pulmonary TB decreased by 8% per year, double the rate before DOTS was introduced [113,133,134].

The tuberculosis control programme of Beijing, China has used direct observation of treatment since 1979, and has shown a substantial and progressive decline in tuberculosis cases (87% reduction in prevalence from 1979 to 1990), deaths (80% reduction), and a 9% annual decrease in new smear-positive cases was documented between 1986 and 1996. Drug resistance has remained minimal [135]. Between 1990 and 2000, TB prevalence decreased by 32%-37% in areas where the DOTS Strategy was implemented [115].

Nontheless, more than a decade after the launch of the DOTS Strategy, the number TB cases worldwide continues to rise [2]. In many countries such as Benin, Cambodia, remaining parts of China, Malawi, Nicaragua, and the United Republic of Tanzania, no impact is seen despite remarkable results in terms of high cure rates [114,136-141]. In these countries, case detection rates were estimated to be below 70%, but there is doubt as to whether these CDRs were indeed low.

Is then DOTS in many countries inadequate as a TB control strategy, and if so, why?

Much effort, political commitment and funding have invested to implement the DOTS Strategy not only at global level but also at national level in many countries over past 10 years. Thus, it is important to establish whether DOTS programmes have impact on the TB epidemic. If not, different or additional control interventions may have to be developed and implemented.

Among the 22 countries with the highest burden of TB cases, Vietnam is thus far the only one that has consistently reported case detection rates and cure rates above the WHO targets over the last years [2]. However, TB case notification rates in Vietnam as reported to WHO show no decline. This makes Vietnam an important setting for closely studying the impact of the DOTS Strategy on the TB epidemic.

This can be done by analyzing trends in routine TB notification data and comparing these to trends in annual risk of infection, on which data are available from repeated tuberculin surveys among school children in sentinel provinces.

Lack of impact despite meeting the WHO targets might be due to erroneous estimate of case detection and cure rates. The CDR is not easily measured since in Vietnam, as in most other high-burden countries, the true incidence of TB is unknown. An estimate of the CDR is therefore derived from the same models on which the WHO targets were based [127]. Direct estimates of the case detection rate can be obtained by population surveys of prevalent pulmonary TB (i.e. prevalence surveys) [142]. Such a survey was planned for Vietnam, but since this was delayed, alternative ways needed to be sought to make an indirect assessment of the quality and completeness of case detection.

Relevant indicators for such an assessment are the proportion of the adult population that has sputum smear examination annually at the district TB units (DTU), and the proportion of these patients who have a positive smear [143] By assessing their distribution by age, sex, geography, socio-economic status and traveling distance to the DTU, patterns of high and low case detection can be identified.

Another indicator is diagnostic delay, i.e. the period between onset of disease (i.e. of infectiousness), and diagnosis and start of treatment. Early case detection is important in order to reduce the transmission of TB [67]. Both theory [132,144] and practice [145,146] suggest that incidence and death rates could be forced down quickly if diagnostic and treatment delays, and hence the average duration of infectiousness, are shortened. If this delay is long, even high CDRs may not result in sufficient reduction of TB transmission [147]. Thus, short delays point to high CDR, and analysis of risk factors for long delays may help identify segments of the patient population for which case detection should be improved.

The cure rates of the NTP are based on routine treatment outcome monitoring. Since inadequate DOTS contributes to increased rates of relapse and drug resistance, independent verification of the cure and failure rates can be sought by follow-up of TB patients after successful treatment for relapse, and by assessing the trend of the prevalence of (multi)drug resistance among TB patients before treatment initiation. These indicators are independent of the quality of the routine surveillance of treatment outcomes [37,43,148].

To answer the question whether a DOTS program in a high-burden country that meets the WHO targets of at least 70% case detection and at least 85% cure has an impact on TB transmission and disease burden or not, this study focused on two aspects: 1/ The quality

and completeness of case detection by the Vietnamese National Tuberculosis Control Program. This was done using the following indicators: diagnostic delays among newly diagnosed smear-positive TB patients; use and yield of sputum smear microscopy by age and sex; geographic patterns of the proportion of the population examined and the proportion of smear-positives; 2/ The impact of control on the TB epidemic was assessed using the following indicators: trends in case notification and annual risk of TB infection (ARTI) in 6 sentinel provinces; extent of relapse among patients successfully treated for new smear-positive pulmonary tuberculosis; and prevalence of drug resistance among TB patients and its trend over time.

**TUBERCULOSIS AND TUBERCULOSIS CONTROL IN VIETNAM**

Vietnam is a South East Asian country with an area of 330.000 sq. km that stretches 3,260 km along the eastern coast of the Indochina peninsula. It borders China in the north and Laos and Cambodia in the west. Three great geographical features dominate the country: the Red river in the North, the Mekong river in the South and the central highland in between. Mountains and hills cover four-fifths of the territory. There are two different climatic zones in Vietnam. Northern Vietnam has 4 distinct seasons, spring, summer, autumn and winter. Southern Vietnam has 2 seasons, dry and wet.

The estimated total population of Vietnam in 2005 was 84 million. About 39% of the population was in the age group under 15 years, and 5% in the age group 65 years or more. The average annual population growth over the period 1995-2000 was 2.1%.

In 2004, 20% of the Vietnamese population lived below the poverty line [149]. Ethnic minorities account for 13% of the country's population. Whereas the majority Kinh population inhabit mainly the fertile lowlands in the river deltas and along the coast, these minorities mainly live scattered across the mountain areas that cover two-thirds of the country's territory, extending from the north to the south. The largest city is Ho Chi Minh City in the South with a population of about 5 million. The capital Hanoi, located in the North, has a population of about 2.5 million [150].

Administratively, there are four levels in the country: central, city/provincial, district and commune. Vietnam has 60 provinces and 4 centrally administered cities, 631 districts (about 130,000 inhabitants each), 10,553 communes (about 7,000-9,000 inhabitants each) and 104,146 villages.

Agriculture employs 70% of the labor force and contributes over 50% of the gross domestic product (GDP). The main crop is rice. Over the past ten years Vietnam recorded many achievements in economic reform and a high rate of economic growth in the decade from 1991-2000. The structure of the economic sector is changing in line with market mechanisms. The average annual growth rate of GDP was 7.5%. There is evidence suggesting that income inequity has been rising.

In May 2002 the Government published the Comprehensive Poverty Reduction and Growth Strategy (CPRGS). This Strategy is an action plan that translates the Government's Ten-Year Socio-economic Development Strategy, Five-Year Socio-economic Development Plan as well as other sectoral development plans into concrete measures with well-defined road maps for implementation. The health agenda of the CPRGS is to promote the grass-roots health system, maintain and develop health services; to give priority to against diseases that affect the poor (reproductive health, infectious diseases, HIV/AIDS, children's diseases and other "social" illnesses); to improve the quality of health services and provide support to the poor with health services subsidies.

Although Vietnam is among the 30 poorest countries in the world, basic health indicators are much better than those in countries with the same per capita GDP. The table below shows some basic health indicators.

**Table 1. Population, social and economic, environment indicators (2003)**

| | |
|---|---|
| Population (2005) | 84 |
| Population density (persons/$Km^2$) | 245 |
| Population growth rate (%) | 1.5 |
| Percentage of urban population (%) | 25.8 |
| GDP (Billion VND) | 605,491 |
| GDP per capita ('000 VND) | 7,484 |
| Expenditure of state budget (Billion) | 172,246 |
| Health budget (Billion) | 7,751 |
| % Health budget in GDP | 1.28 |
| % Health budget in state budget expenditure (%) | 4.5 |
| Health budget per capita ('000VND) | 95.8 |
| % Malnutrition on height of children under 5 years old | 32.0 |
| % Malnutrition on height of weight of children under 5 years old | 28.4 |
| Birth weight under 2500grs (%) | 6.5 |
| % of people used safe water | 70.1 |
| Life expectancy | 70 |
| - Male | 68 |
| - Female | 72 |
| Infant mortality rate (o/oo) | 30.0 |
| Literacy rate | 91.1 |
| - Male | 94.3 |
| - Female | 88.2 |

*Source: Health statistics Yearbook – 2003 [150]*
*1USD ~ 16,000 Viet Nam Dong (VND)*

In 2000 the health services comprised 13,051 facilities, including 817 hospitals and 11,117 health stations of which 10,307 at the commune level. The number of inhabitants per doctor and nurse is 1,859 and 1,780 respectively. Little is known about the total size of the private

sector in the health services market and its growth over the past 10 years. Traditional health services still play an important role in Vietnam.

The Ministry of Health divides the country into the 8 health regions: Red River delta, North East Region, North West Region, North Central Coast Region, South Central Coast Region, Central Highlands Region, East South Region, Mekong River Delta Region). The regions have distinct characteristics as regards geographical situation, accessibility, and population density and development indicators.

In recent years Vietnam has experienced a rapidly expanding HIV epidemic. As of 31 December 2006, a total of 114,367 cumulative cases of HIV infection, 19,695 cases of AIDS, and 11,468 deaths due to AIDS had been officially reported. It is estimated that more than 280,000 cases of HIV exist in the country. HIV infection has been identified in all 64 provinces of the country (unpublished data, AIDS Division, Ministry of Health, 2006). Of the reported cases in 2003, 85% were male, 51% reported injection drug use (IDU), followed by female sex workers (1.3%) and sexually transmitted disease patients (1.0%). 83% were aged 20 to 39 years at the time of HIV diagnosis. There was an increasing number of young people under 30 years in reported HIV cases over the last years, from 22% in 1995 to 70% in 2002 [151]. HIV/AIDS sentinel data showed that 4.8% of TB patients were HIV positive in 2004. More than 10 provinces had greater than 5% prevalence of HIV among TB patients [unpublished data, AIDS Division, Ministry of Health, 2004].

After independence tuberculosis control started in Vietnam in 1957 with the establishment of the National Institute of Tuberculosis in Hanoi and the National TB Control Program in the South. Since the reunification in 1975 the National Institute in Hanoi is responsible for the National TB Program. During the period 1975-1985 the TB control program missed a clear strategy to address the problem of TB and suffered from lack of funds to purchase drugs.

In 1986 the program adopted the TB control strategy of the International Union Against Tuberculosis and Lung Disease (IUATLD) and WHO and started to introduce DOTS. The objective of the NTP in Vietnam is to reduce TB morbidity, mortality and transmission and to prevent emerging of TB drug resistance in the community. Full-scale countrywide coverage of DOTS became only possible when the Government declared TB control a national priority in 1995.

The tuberculosis control network covers all four administrative levels and the integration of tuberculosis control activities and other general medical activities at primary level.

At the national level the director of the National Hospital for Tuberculosis and Respiratory Disease (NHTRD) in Hanoi is responsible for the NTP. The director is answerable to the Minister of Health. The Pham Ngoc Thach hospital in Ho Chi Minh City has delegated responsibility for TB control in 22 southern provinces. Both hospitals are responsible for the overall implementation of the NTP in the provinces including training, drug distribution

and supervision. They also act as reference laboratories and are responsible for the quality control of the laboratories at the peripheral levels

At the provincial level exists either a TB center or TB ward as part of the provincial general hospital. Each province has a TB control team headed by the Provincial TB Coordinator (PTC).

The provincial TB centres and Tuberculosis Units are responsible for implementation of the tuberculosis program in the provinces and districts respectively. The provincial tuberculosis coordinator gives close guidance to the districts, supervises training activities, data collecting and the distribution and proper use of drugs. The tuberculosis district unit is responsible for confirmation of the diagnosis by microscopy, initiation of the ambulatory treatment at communes near the patient's home, and supervision of the conduct of the NTP in the communes.

At the commune level, a general staff is responsible for communicable diseases including tuberculosis. Health workers are responsible for community health care including TB and in the villages. The commune and village levels identify and refer TB suspects to the districts and provide ambulatory treatment for TB.

In 2000, the total staff involved in TB control was 15,772 [153].

Vietnam is one of the seven countries with a high burden of TB in the Western Pacific region. It also ranks 13th on the list of the 22 high TB burden countries in the world [2].

**Table 2. Estimated burden of tuberculosis in Vietnam in 1997 and 2005**

| | 1997 [4] | 2005 [2] |
|---|---|---|
| Population (million) | 76.5 | 84.2 |
| Annual Risk of infection (%) | 1.7 | |
| Incidence (all cases/100 000 pop/year) | 145 | 175 |
| Incidence (new ss+/100 000 pop/year) | 65 | 79 |
| Prevalence (all cases/100 000 pop) | 221 | 235 |
| TB mortality (all cases/100 000 pop/year) | 20 | 23 |
| HIV prevalence in incident TB cases (%) | | 3 |
| MDR-TB (%) [148] | 2.3 | |

Vietnam was the first high TB burden countries to achieve the TB control targets. The NTP of Vietnam introduced DOTS in 1986 and achieved 100% DOTS coverage and the WHO targets for case detection and treatment success since 1997 [2].

## STRUCTURE OF THIS THESIS

**Chapter 1** provides an overview of the global TB burden, natural history of tuberculosis, measuring the impact of TB control as well as TB and TB control in Vietnam. The rationales and general objectives of the study are given. **Chapter 2** describes trends in case notification and treatment outcomes of tuberculosis patients diagnosed and treated in the NTP since its inception in 1986. **Chapter 3** assesses diagnostic delay among TB patients diagnosed within the NTP in a nationwide representative survey. **Chapter 4** assesses the use and yield of sputum smear examination by the NTP, and its variation by age and sex with emphasis on gender differences in access to care, in a representative survey in the northern part of Vietnam. In **chapter 5** the variation in TB notification by analyzing notification rates of smear-positive TB in Vietnam by individual commune during one quarter in 2003 is presented. **Chapter 6** estimates the trends in annual risk of tuberculosis infection, and compares these to trends in case notification rates from repeated tuberculin surveys in 6 sentinel provinces. **Chapter 7** assesses the relapse rate after 12-24 months among new smear positive pulmonary TB patients who completed treatment in the northern part of Vietnam. **Chapter 8** presents the prevalence of drug resistance among TB cases diagnosed with and without a history of previous TB treatment, and compares this to the results of the previous survey in another nationwide survey. Finally, in **chapter 9** contains the main findings of the studies, general discussion and recommendation for TB control and further research.

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# Chapter 2

# Establishment and development of the National Tuberculosis Control Programme in Vietnam

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**ABSTRACT**

*Objective*: To describe the establishment and development of the National tuberculosis Control Programme (NTP) of Vietnam.

*Methods*: Data were obtained from the surveillance system established by the new NTP in 1986 and based on the principles now described as the WHO DOTS Strategy.

*Results*: The proportion of districts covered by the NTP increased from 40% in 1986 to almost 100% in 2000. The proportion of communes applying NTP guidelines increased from 18% in 1986 to 99.8% in 2000. The total number of tuberculosis cases notified increased from 8737 in 1986 to 89 792 in 2000. Most of these are new smear-positive cases. Based on WHO estimations of the incidence rate, the proportion of new smear-positive cases detected and put on short-course treatment has been over 70% since 1996. Reported cure rates with short-course chemotherapy are consistently over 85%.

*Conclusions*: DOTS is feasible in a low-income, high-burden country. The main reasons for success were political commitment, a well-functioning health network, integration of tuberculosis control into the general health service at district level, a continuous supply of drugs and effective external support. Major challenges are long-term financial support, expansion to remote areas and vulnerable groups, definition of the role of the private sector, and future developments of the HIV epidemic and multidrug resistance.

## INTRODUCTION

Vietnam is among the 22 countries with the highest number of tuberculosis cases in the world [1]. In 2002, 95 577 cases were notified to the World Health Organization (WHO), giving a total case rate of 115 per 100 000 population [2] The prevalence of infectious tuberculosis in Vietnam in 1997 was estimated at 102/100 000, and the incidence at 85/100 000, with 20 000 deaths from tuberculosis (TB) annually [1]. In a survey in 1996, 2.3% of new smear-positive tuberculosis cases had multidrug-resistant strains [3,4]. Until 2000 the prevalence of human immunodeficiency virus (HIV) infection was low, <4% among tuberculosis patients in Ho Chi Minh City in 1995–2000 [5].

Vietnam is the only high-burden country to have reached the WHO targets of 70% case detection rate and 85% cure rate [2].

Tuberculosis control activities in Vietnam started in 1957, with separate systems in the North and the South. After the reunification of Vietnam in 1975, the National Institute for Tuberculosis in Hanoi established national guidelines for tuberculosis control as well as for specialized clinical care. Implementation of these guidelines was decentralized at district level. The cure rate did not exceed 40%.

A new national tuberculosis control programme (NTP) was introduced in 1986. Its policies, which were established in 1985, antedated the present WHO DOTS Strategy [6] and followed IUATLD principles: 1) direct smear examination as the main diagnostic method for persons who present to the health service with symptoms suggestive of tuberculosis disease; 2) a uniform treatment regimen throughout the country; 3) continuous monitoring of case finding and treatment results; and 4) integration of tuberculosis control activities into the general health system at primary health care level (district and commune level).

In this paper we describe the establishment and development of the Vietnam NTP. Emphasis is given to changes in the case detection and cure rates over time, associated with the introduction of short-course chemotherapy and increasing geographic coverage.

## METHODS

Data on tuberculosis case finding and treatment were obtained from the surveillance system established by the NTP in 1986. Population data were available from 10-yearly population censuses, the last of which was conducted in 1999. Data were processed using Epi Info V 6 (CDC, Atlanta, GA, USA) and maps were made using Epi Map (www.cdc.gov).

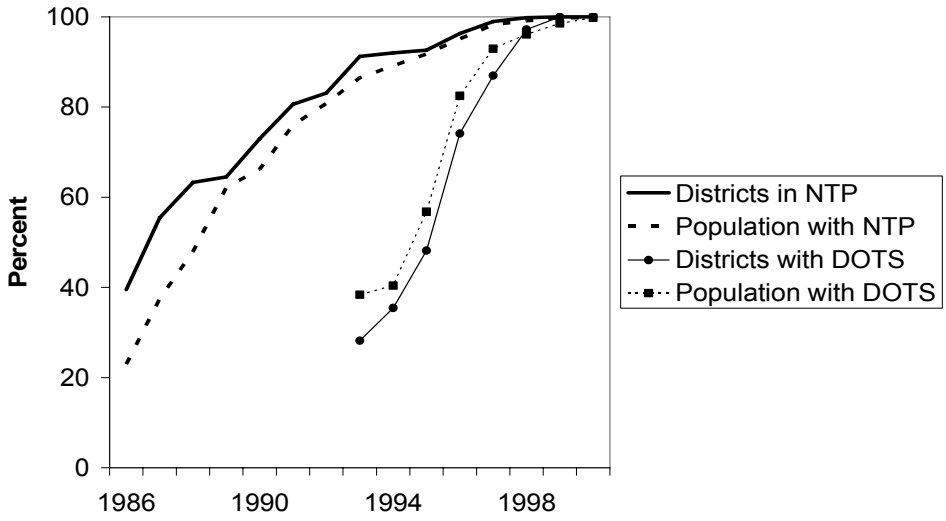
## RESULTS

The proportion of districts covered by the NTP increased from 40% in 1986 to 100% in 2000 (Figure 1). Within districts, training of communal health workers and provision of supplies expanded so that the proportion of communes applying NTP guidelines increased

from 18% in 1986 to 99% in 2000. The population that has access to a unit implementing the NTP guidelines increased from 23% in 1986 to 99.8% in 2000 (Figure 1).

Short-course chemotherapy (SCC) using 2SHRZ/6HE was first introduced in 1989 in 12 districts of four provinces. The proportion of districts applying SCC was 28% in 1993, 50% in 1995, 87% in 1997 and 100% from 1999 onward (Figure 1).

**Figure 1. Coverage of NTP activities and DOTS by districts and total population in Vietnam, 1986-2000. NTP = National Tuberculosis Control Programme**




During the first year that the NTP was operational, only 8737 TB cases were detected. This number rose quickly to 41 000 in 1989 and 56 000 in 1992 (Table 1). At this point, drug supply could not keep up with the expansion of the programme and case notification decreased slightly for 2 years, picking up again when the government gave the NTP high priority among health care programmes and additional support was received from the Dutch government. After subsequent input by the World Bank and the introduction of a bonus system in 1996, a further increase in notifications was observed to around 89,000 patients detected in 1999 and 2000.

The national notification rate for new smear-positive patients increased from 11 per 100 000 population in 1986 to a peak of 73 in 1998 and decreased slightly to 69 in 2000 (Table 1). Mapping notification rates by province suggests a North-South gradient, with higher rates in the South than in the North (Figure 2). Notification rates increased with the expansion of the programme (Figure 2). These remained low in the mountainous provinces

of the central highlands and the north-west provinces, suggesting a lower tuberculosis incidence in those areas, or, perhaps more likely, under-detection of tuberculosis.

**Table 1. Tuberculosis notification rates and case-detection rates in Vietnam by year, 1986-2000**

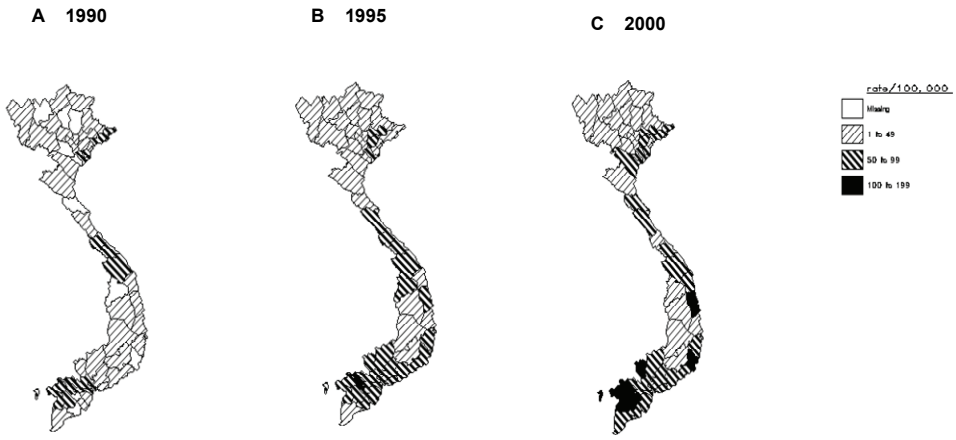
| Year | PTB Smear-positive New | PTB Smear-positive Relapse | Smear-negative cases | EPTB cases | Total | SCC* (%) | Rate new smear+/ 100 000 | CDR (%) # |
|---|---|---|---|---|---|---|---|---|
| 1986 | 6,645 | 510 | 1,157 | 425 | 8,737 | 0 | 11 | 13 |
| 1987 | 17,355 | 2,457 | 2,235 | 1,572 | 23,619 | 0 | 29 | 34 |
| 1988 | 22,749 | 3,489 | 5,259 | 3,816 | 35,313 | 0 | 37 | 44 |
| 1989 | 27,192 | 3,183 | 6,429 | 4,257 | 41,061 | 4 | 43 | 50 |
| 1990 | 30,728 | 3,627 | 7,971 | 5,210 | 47,536 | 7 | 47 | 56 |
| 1991 | 35,865 | 4,112 | 8,270 | 6,262 | 54,509 | 17 | 54 | 63 |
| 1992 | 38,659 | 4,221 | 7,569 | 6,145 | 56,594 | 28 | 57 | 67 |
| 1993 | 36,534 | 3,818 | 6,812 | 5,830 | 52,994 | 36 | 52 | 61 |
| 1994 | 35,613 | 3,764 | 6,946 | 5,440 | 51,763 | 46 | 50 | 59 |
| 1995 | 37,550 | 3,616 | 8,379 | 6,194 | 55,739 | 58 | 52 | 61 |
| 1996 | 48,911 | 4,936 | 12,761 | 8,103 | 74,711 | 78 | 68 | 80 |
| 1997 | 50,016 | 4,966 | 14,629 | 8,327 | 77,938 | 93 | 68 | 80 |
| 1998 | 54,889 | 5,142 | 17,205 | 10,232 | 87,468 | 96 | 73 | 86 |
| 1999 | 53,805 | 5,400 | 17,729 | 11,945 | 88,879 | 99 | 71 | 83 |
| 2000 | 53,169 | 5,493 | 17,993 | 13,137 | 89,792 | 100 | 69 | 81 |

* Percentage of patients registered for SCC.
# Annual new smear-positive cases notified divided by estimated incidence [1]
PTB = pulmonary tuberculosis; EPTB = extra-pulmonary tuberculosis; SCC = short-course chemotherapy; CDR = case detection rate.

To estimate the proportion of new tuberculosis cases detected by the programme, we used the WHO estimate of tuberculosis incidence [1]. The proportion of the expected number of smear-positive cases detected by the programme was stable, at around 60% in the years 1991–1995, indicating that the programme was keeping up with population growth but not expanding beyond that. This proportion increased to 80% in 1996, reached 86% in 1998, and declined again slightly to 83% in 1999 and 81% in 2000 (Table 1). This slight decline in notification rates may indicate declining case detection or declining incidence. The proportion of smear-positive cases on treatment receiving SCC was 4% in 1989, 58% in 1995 and 95% in 2000.

The cure rate of long-course chemotherapy (3SHZ/6H2S2) improved from 62% in 1987 to 79% in 1997, while the proportion defaulting fell from 15% to 5% during the same period (Table 2). The proportion of patients reportedly dying during treatment decreased from 5% in 1989 to 3% in 1997, while the proportion of treatment failures fell from 6% in 1986 to 3% in 1997. Overall, 69% of smear-positive patients were reported cured by the long-course treatment regimen.

**Figure 2. Notification rates of new smear-positive tuberculosis in Vietnam in 1990 (A), 1995 (B), and 2000 (C).**




SCC cure rates were initially around 15% higher than those of long-course chemotherapy and have been stable, at 88–90% (Table 3). The proportion of patients who complete treatment without a sputum test has been low and has remained well below that for long-course treatment. Reported failure has been below 1.5% since 1995. The proportion of patients reported defaulting from treatment has been <3% since 1993, while the proportion reported as transferred out has been ≤3% throughout. Case fatality was somewhat lower among patients on SCC than among those on long-course chemotherapy (Tables 2 and 3).

The average cure rates for new smear-positive patients on long-course and SCC, weighted according to the relative number of patients treated with each, was 70% in 1986, 80% in 1994, 85% in 1996, and 90% in 1999 and 2000. Maps of province-specific cure rates show that in 1990 none of 46 provinces achieved the target cure rate of 85% (Figure 3). This proportion increased to 21 of 53 provinces in 1995 and 56 of 61 provinces in 2000 (Figure 3). The minimum cure rate observed in any province increased from 0% in 1990 to 26% in 1995 and 65% in 2000.

**Table 2. Treatment results for new smear-positive tuberculosis cases by long-course regimen ($3SHZ/6H_2S_2$)* in Vietnam, 1986-1999**

| Year | Registered for treatment n | Cured (%) | Treatment Completed (%) | Died (%) | Failure (%) | Lost (%) | Transfer Out (%) |
|---|---|---|---|---|---|---|---|
| 1986 | 6,539 | 70 | 9 | 4 | 6 | 9 | 3 |
| 1987 | 16,879 | 62 | 12 | 3 | 6 | 15 | 3 |
| 1988 | 22,403 | 65 | 8 | 4 | 7 | 12 | 4 |
| 1989 | 25,213 | 64 | 9 | 5 | 6 | 12 | 3 |
| 1990 | 27,878 | 68 | 10 | 4 | 6 | 10 | 3 |
| 1991 | 27,109 | 69 | 10 | 4 | 5 | 9 | 3 |
| 1992 | 27,254 | 70 | 11 | 4 | 4 | 8 | 3 |
| 1993 | 23,208 | 69 | 11 | 4 | 4 | 9 | 3 |
| 1994 | 19,644 | 75 | 9 | 3 | 4 | 7 | 2 |
| 1995 | 16,249 | 76 | 9 | 3 | 3 | 6 | 2 |
| 1996 | 10,278 | 77 | 9 | 3 | 3 | 6 | 2 |
| 1997 | 3,585 | 79 | 8 | 3 | 3 | 5 | 2 |
| 1998 | 1,752 | 75 | 10 | 4 | 2 | 6 | 2 |
| 1999 | 46 | 85 | 9 | 4 | 0 | 2 | 0 |
| Total | 228,037 | 69 | 10 | 4 | 5 | 10 | 3 |

* Numbers before the letters indicate the duration in months of the phase of treatment; numbers in subscript indicate the number of times the drugs are taken each week.
S = streptomycin; H = isoniazid; Z = pyrazinamide.

The NTP treated 543 151 new smear-positive patients in the first 15 years of its existence and reportedly cured 438 343 cases. If, in the absence of treatment, at least half of smear-positive patients would have died [7], the programme averted over 250 000 deaths in its first 15 years.

## DISCUSSION

By the end of 2000, approximately 99% of the population of Vietnam lived in towns and villages that were reached by the NTP. At this point, it was estimated that there were almost 67 000 new infectious cases of tuberculosis. Based on programme reports, approximately 80% of these were detected, of whom 93% successfully completed treatment. Vietnam is at present the only country among the 22 high-burden countries that reaches the WHO targets for tuberculosis control [2].

**Table 3. Treatment results for new smear-positive tuberculosis cases by short-course regimen (2SRHE/6EH)* in Vietnam, 1989-2000**

| Year | Registered for treatment n | Cured (%) | Treatment Completed (%) | Died (%) | Failure (%) | Lost (%) | Transfer Out (%) |
|---|---|---|---|---|---|---|---|
| 1989 | 1,147 | 85 | 2 | 2 | 4 | 7 | 0 |
| 1990 | 2,135 | 86 | 1 | 2 | 3 | 7 | 1 |
| 1991 | 6,206 | 90 | 1 | 2 | 2 | 3 | 2 |
| 1992 | 10,950 | 88 | 1 | 3 | 2 | 3 | 3 |
| 1993 | 12,975 | 88 | 1 | 3 | 2 | 3 | 2 |
| 1994 | 16,246 | 89 | 2 | 3 | 2 | 2 | 3 |
| 1995 | 21,879 | 89 | 2 | 3 | 1 | 2 | 2 |
| 1996 | 37,996 | 87 | 3 | 3 | 1 | 2 | 3 |
| 1997 | 46,466 | 88 | 3 | 3 | 1 | 2 | 2 |
| 1998 | 52,749 | 90 | 3 | 3 | 1 | 2 | 2 |
| 1999 | 53,224 | 90 | 2 | 3 | 1 | 2 | 2 |
| 2000 | 53,138 | 90 | 2 | 3 | 1 | 2 | 2 |
| Total | 315,111 | 89 | 3 | 3 | 1 | 2 | 2 |

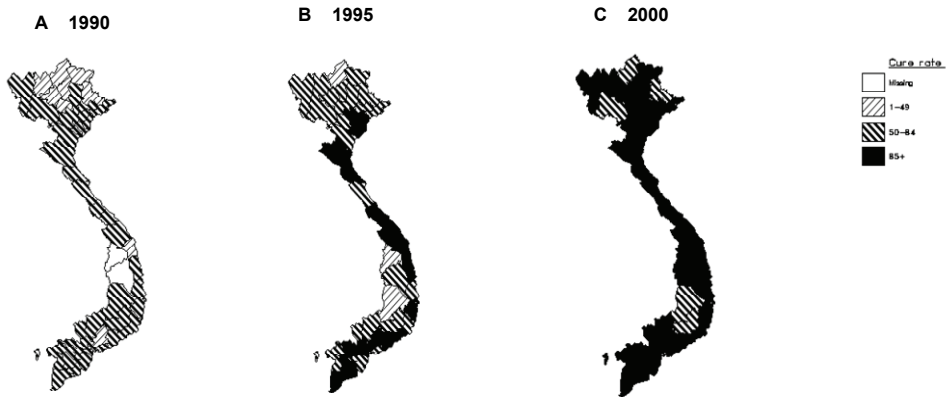
* Numbers before the letters indicate the duration in months of the phase of treatment.
S = streptomycin; R= rifampicin; H= isoniazid; E = ethambutol.

Many factors have contributed to the success of tuberculosis control. The Government of Vietnam, from central to local level, has shown strong political commitment. Effective tuberculosis control is part of the Comprehensive Poverty Reduction and Growth Strategy, and tuberculosis control is contributing to the attainment of the Millennium Development Goals for poverty reduction in Vietnam. Tuberculosis control activities at district and commune level are fully integrated into the general health care system. TB drugs, laboratory reagents, equipment and means of transport, however, have been supplied by the NTP directly to the provincial TB centres and from there directly to the district TB units. In addition to government support, the NTP has received major sustained technical and financial assistance from international organizations.

Despite this success, the NTP faces several challenges. In the coming decade, it will need to deal with a rapid increase in TB cases with HIV co-infection, problems resulting from urbanization and emerging private practice, and problems of low coverage of DOTS in remote and mountainous areas, TB in prisons, and TB among the elderly and in psychiatric patients. Other challenges to the NTP include how to consolidate success in the expansion

of DOTS, how to maintain case holding and high-quality monitoring, and the consideration of human rights aspects, equality and equity in providing health care services.

**Figure 3. Cure rates of new smear-positive tuberculosis in Vietnam in 1990 (A), 1995 (B), and 2000 (C).**




The data reported in this paper have limitations associated with routine surveillance data. As treatment outcome is in principle known for all notified cases, the numbers of cases detected in a given year should equal the numbers evaluated for treatment outcome, although slight differences may occur due to administrative errors. The number of cases not evaluated as a proportion of the cases detected fluctuated between 1% and 3% between 1986 and 1990, peaked at 7% in 1991 due to administrative reorganization in seven provinces, and subsequently declined to 0.5–1.5% in the years 1992–2000.

What the reported data do not show is the number of patients who are diagnosed in the laboratory but who are not treated, as cases are entered into the district tuberculosis register at the time they start treatment. These data have been recorded by the NTP since 2000, and data for 2000 suggest that less than 5% of persons detected by direct microscopy are not registered for treatment.

An incentive system introduced in 1996 plays an important role in motivating the NTP staff to improve both case detection and treatment supervision. In the densely opulated lowlands, laboratory workers receive the equivalent of $0.70 for each positive smear and community health workers $3.50 for each tuberculosis patient cured. These mounts are doubled in the sparsely populated highlands. Notification rates increased as well as cure rates. However, the bonus system may encourage some health workers to declare people as TB patients who

never had the disease. Quality control of the laboratories should counteract this danger. Similarly, workers may be tempted to declare a patient as cured, i.e., reading smears too superficially at the end of treatment or not reading them at all. However, the data show that the proportion of patients completing treatment without a smear result is small.

Based on the experience reported in this paper and in other countries such as Tanzania [6] China [8] and India [9] we conclude that the DOTS Strategy is feasible in a low-income, high-burden country.

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# Chapter 3

# Delays in the diagnosis and treatment of tuberculosis patients in Vietnam: a cross-sectional study

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**ABSTRACT**

*Background:* Treatment delay is an important indicator of access to tuberculosis diagnosis and treatment. Analyses of patient delay (i.e. time interval between onset of symptoms and first consultation of a health care provider) and health care delay (i.e. time interval between first consultation and start of treatment) can inform policies to improve access. This study assesses the patient, health care provider and total delay in diagnosis and treatment of new smear-positive pulmonary tuberculosis patients, and the risk factors for long delay, in Vietnam.

*Methods:* A cross-sectional survey of new patients treated by the National Tuberculosis Control Programme was conducted in 70 randomly selected districts in Vietnam. All consecutively registered patients in one quarter of 2002 were interviewed using a pre-coded structured questionnaire.

*Results:* Median (range) delay was 4 weeks (1-48) for total, 3 (1-48) weeks for patient and 1 (0-25) week for health care delay. Patients with long total delay (≥12 weeks, 15%) accounted for 49% of the cumulative number of delay-weeks. Independent risk factors ($p<0.05$) for long total delay were female sex, middle age, remote setting, residence in the northern or central area, and initial visit to the private sector. For long patient delay (≥6 weeks) this was female sex, belonging to an ethnic minority, and living at >5 km distance from a health facility or in the northern area. For long health care delay (≥6 weeks) this was urban setting, residence in the central area and initial visit to a communal health post, TB hospital or the private sector.

*Conclusion:* Analyses of patient and treatment delays can indicate target groups and areas for health education and strengthening of the referral system, in particular between the private sector and the NTP.

## BACKGROUND

Delays in diagnosis and treatment of tuberculosis (TB) are common. They may reflect patient delays in seeking care, health care provider delays in making the diagnosis and starting treatment, or both [1-7].

Diagnostic delay may result in more advanced and severe disease, higher mortality and sustained spread of *M. tuberculosis* in the community as untreated persons continue to transmit the infection to others [8,9]. Information on diagnostic delay and its trend over time is thus important for evaluation and improvement of TB control programmes.

Distributions of diagnostic delays tend to be skewed: they are relatively short for most TB patients, but very long for some [3,4]. Patients with long diagnostic delays may therefore contribute disproportionately to the cumulative delay of all patients and thereby, potentially, to TB transmission. Prevention of these long delays could therefore be more effective in curbing TB transmission than further reduction of the median delay among all patients. Therefore, it is also important to know the risk profile of patients with long diagnostic delays.

Vietnam is among the 22 countries with a high TB burden. In 2002, the National Tuberculosis Control Program (NTP) detected 95 044 TB cases (118 per 100 000 population), including 56 811 (71/100 000) new smear-positive cases [10,11]. From 1997 onwards, the estimated case detection rate of the NTP has been above the WHO target of 70%. One would thus expect diagnostic delays to be relatively short, but no nationally representative data are available. A study in 4 provinces in Vietnam in 1996 showed a mean total delay among TB patients of 12 weeks [12]; only small-scale studies of delay have been published since [13,14,15]. In these studies, women had longer delays than men, and more often had visited less qualified health care providers before a diagnosis of TB was made [12-15]. In the NTP, the district is the key level for diagnosis and treatment. Patients with TB symptoms can choose any (private or public) health care provider or go directly to the district TB unit (DTU). Referral to the DTU by private health care providers tends to be limited [16]. The growth of the private health sector may thus affect diagnostic delays [17,18].

We performed a nation-wide study of diagnostic delays in 70 randomly selected district TB units, with the aims of assessing the extent of delay in case-finding and treatment among TB patients diagnosed within the NTP, and identifying risk factors associated with long delay, in particular related to choice of initial health care provider.

## STUDY POPULATION AND METHODS

Eligible were all patients who were registered with newly diagnosed smear-positive pulmonary TB in the third quarter of 2002 in 70 district TB units. These districts had been sampled for a national TB prevalence survey. Sampling was with probability proportional to population size after stratification by area, so that 20 urban, 20 remote and 30 rural

districts were selected. Excluded were patients with permanent or temporary residence outside the district.

Patient delay was defined as the period between the onset of cough and the patient's first attendance of a health care facility because of this cough. Health care provider (HCP) delay was defined as the period between the patient's first attendance of a health care facility with cough, and the onset of treatment. Treatment delay was defined as the period between diagnosis of smear-positive pulmonary TB and the onset of treatment. Total delay was combined patient and HCP delay. Delay periods were recorded in weeks, rounded to the nearest integer value. Long patient delays and health care provider delays were defined as 6 weeks or more and long total delay as 12 weeks or more.

Patients were interviewed using a pre-coded structured questionnaire including demographic variables (age, sex, ethnicity, education and distance from the patient's house to the first health care provider); time period between onset of cough and first contact with health care provider; time period between onset of cough and start of treatment; date of diagnosis; starting date of treatment. The district TB coordinators were trained to perform interviews and interviewed patients within 2 weeks of treatment registration. The study protocol was approved by the Scientific and Ethical Board of the National Hospital (then: Institute) of Tuberculosis and Respiratory Diseases, Hanoi.

Data were double entered using Epi Info v6; inconsistencies were checked against the raw data. Data were analyzed using Stata v8. The chi-square tests were used to compare differences in proportions in total delay between subgroups. Because delays had non-normal distributions, Wilcoxon Rank Sum and Kruskal-Wallis tests were use to test for significance. Mean delays are nonetheless reported for comparison with other studies. Uni- and multivariate logistic regression analysis was used to identify risk factors that were associated with long delay. We tested for significance using the likelihood ratio test for comparing the model likelihood with and without the variable or interaction term of interest.

**RESULTS**

During the study period, 2,093 smear positive pulmonary TB patients were registered and interviewed. Among the subjects interviewed, 1898 (92%) patients were interviewed within one week after starting treatment. Of the study subjects, 1491 (71%) were male. The male-to-female ratio (2.5:1) reflected the male-to-female ratio of notified smear positive pulmonary patients in Vietnam in 2002 (2.4:1, NTP unpublished data). Information on total, patient and HCP delay was available for 2069 (99%), 2,075 (99%) and 2034 patients (97%), respectively.

Mean total delay was 7.5 weeks with a median of 4 weeks (range: 1-48). Total delay tended to be longer among women and with increasing age, as well as in the northern part of the country, in rural and remote districts settings, among ethnic minority groups and among patients who presented initially to a pharmacy or a communal health post (Table 1).

**Table 1. Characteristics of, and total delays among 2093 new smear-positive pulmonary tuberculosis patients in Vietnam.**

| | N (%) | Total delay in weeks | | | Percentage due to patient delay |
|---|---|---|---|---|---|
| | | Mean (95% CI) | P-value | Median (25-75 percentiles) | |
| Time (weeks) | | 7.5 (6.8-7.5) | | 4 (3-8) | 62.7% |
| Sex | | | <0.001 | | |
| Men | 1491 (71.4) | 7.1 (6.4-7.8) | | 4 (3-8) | 62.0% |
| Women | 596 (28.6) | 8.4 (7.4-9.4) | | 5 (4-9) | 66.7% |
| Age (years) | | | 0.001 | | |
| 0-24 | 187 (9.1) | 5.6 (5.0-6.3) | | 4 (3-8) | 60.7% |
| 25-34 | 328 (15.9) | 6.3 (5.4-7.1) | | 4 (3-8) | 61.9% |
| 35-44 | 445 (21.7) | 8.1 (6.1-10.1) | | 4 (3-8) | 58.0% |
| 45-54 | 378 (18.4) | 7.5 (6.5-8.5) | | 4 (3-8) | 68.0% |
| 55-64 | 251 (12.2) | 8.1 (6.7-9.4) | | 5 (3-9) | 66.7% |
| 65+ | 464 (22.6) | 8.2 (6.9-9.4) | | 5 (4-8) | 64.6% |
| Ethnicity | | | 0.048 | | |
| Viet | 1944 (94.0) | 7.4 (6.8-8.0) | | 4 (3-8) | 62.2% |
| Ethnic minority | 124 (6.0) | 8.4 (6.7-10.0) | | 5 (4-9) | 86.9% |
| Education level | | | 0.013 | | |
| Low | 895 (42.9) | 7.5 (6.8-8.2) | | 4 (3-8) | 65.3% |
| Middle | 793 (38.1) | 7.5 (6.8-8.2) | | 5 (3-8) | 64.0% |
| High | 396 (19.0) | 7.3 (5.1-9.5) | | 4 (3-8) | 57.5% |
| Distance from health facility | | | 0.373 | | |
| 0-5 km | 1504 (73.4) | 7.5 (6.7-8.2) | | 4 (3-8) | 57.3% |
| More than 5 km | 544 (26.6) | 7.2 (6.4-8.1) | | 4 (3-8) | 77.8% |
| Health care provider visited initially because of cough | | | <0.001 | | |
| District health center | 339 (16.3) | 6.6 (5.9-7.2) | | 4 (3-8) | 89.4% |
| Commune health post | 620 (29.9) | 9.1 (6.3-11.9) | | 5 (4-8) | 67.0% |
| Public hospital | 360 (17.4) | 5.6 (4.9-6.3) | | 4 (2-6) | 80.4% |
| Pharmacy | 326 (15.7) | 9.0 (8.0-9.9) | | 6 (4-12) | 21.1% |
| Private physician | 339 (16.3) | 7.2 (6.2-8.2) | | 4 (3-8) | 45.8% |
| Traditional healer | 32 (1.5) | 6.7 (5.0-8.4) | | 6 (4-8) | 58.2% |
| Other | 59 (2.8) | 12.7 (6.5-18.8) | | 4 (3-10) | 78.7% |
| Area | | | <0.001 | | |
| Rural | 1029 (49.2) | 8.1 (7.4-8.9) | | 5 (4-8) | 65.4% |
| Urban | 808 (38.6) | 5.8 (5.4-6.2) | | 4 (3-7) | 56.9% |
| Remote | 256 (12.2) | 9.9 (6.4-13.3) | | 5 (3-9) | 71.7% |
| Region (n=2,087) | | | <0.001 | | |
| South | 1316 (62.9) | 5.7 (5.3-6.0) | | 4 (3-6) | 52.6% |
| North | 567 (27.1) | 11.2 (9.3-13.1) | | 6 (4-10) | 81.3% |
| Central | 210 (10.0) | 8.6 (7.2-10.0) | | 5 (4-9) | 44.2% |

**Table 2. Univariate and multivariate analysis of risk factors associated with long delay mong new smear-positive pulmonary tuberculosis patients in Vietnam**

| | Long total delay | | | Long patient delay | | | Long HCP delay | | |
|---|---|---|---|---|---|---|---|---|---|
| | N (%) | OR | aOR* (95% CI) | N (%) | OR | aOR* (95% CI) | N (%) | OR | aOR* (95% CI) |
| Sex | | | | 285/1,476 | | | | | |
| Men | 189/1447 (12.8) | 1 | 1 | (19.3) | 1 | 1 | 169/1449 (11.7) | 1 | 1 |
| Women | 115/586 (19.6) | 1.7 | 1.6 (1.3-2.2) | 149/593 (25.1) | 1.4 | 1.3 (1.0-1.7) | 78/579 (13.5) | 1.2 | 1.2 (0.8-1.7) |
| Age (years) | | | | | | | | | |
| 0-24 | 18/186 (9.7) | 1 | 1 | 30/186 (16.1) | 1 | 1 | 20/184 (10.9) | 1 | 1 |
| 25-34 | 35/323 (10.8) | 1.1 | 1.2 (0.6-2.2) | 60/326 (18.4) | 1.2 | 1.1 (0.7-1.9) | 32/316 (10.1) | 0.9 | 0.9 (0.5-1.8) |
| 35-44 | 72/443 (16.3) | 1.8 | 1.8 (1.0-3.2) | 81/439 (18.5) | 1.2 | 1.1 (0.6-1.8) | 61/434 (14.1) | 1.3 | 1.2 (0.6-2.2) |
| 45-54 | 66/374 (17.7) | 2.0 | 2.1 (1.2-3.8) | 81/375 (21.6) | 1.4 | 1.2 (0.7-2.0) | 44/369 (11.9) | 1.1 | 1.2 (0.6-2.3) |
| 55-64 | 38/249 (15.3) | 1.7 | 1.4 (0.7-2.7) | 61/251 (24.3) | 1.7 | 1.1 (0.7-2.0) | 24/246 (9.8) | 0.9 | 0.9 (0.4-1.9) |
| 65+ | 73/455 (16.0) | 1.8 | 0.9 (0.8-2.6) | 113/458 (24.7) | 1.7 | 1.2 (0.7-2.0) | 65/446 (14.6) | 1.4 | 1.6 (0.8-2.9) |
| Health care provider visited initially because of cough | | | | | | | | | |
| District health center | 78/617 (12.6) | 1 | 1 | 197/620 (31.8) | 1 | 1 | 7/611 (1.2) | 1 | 1 |
| Commune health post | 46/333 (13.8) | 1.0 | 0.9 (0.6-1.4) | 92/339 (27.1) | 0.8 | 0.6 (0.4-0.8) | 22/330 (6.7) | 5.8 | 6.3 (2.6-15.2) |
| Public hospital | 39/357 (10.9) | 0.8 | 1.1 (0.7-1.7) | 77/260 (21.4) | 0.6 | 0.8 (0.6-1.2) | 15/355 (4.2) | 3.2 | 3.3 (1.3-8.3) |
| Pharmacy | 81/322 (25.2) | 2.3 | 4.3 (2.9-6.5) | 18/326 (5.5) | 0.1 | 0.2 (0.1-0.4) | 135/321 (42.1) | 59.0 | 66.0 (29.6-147.3) |
| Private physician | 43/337 (12.8) | 1.0 | 1.7 (1.1-2.6) | 31/339 (9.1) | 0.2 | 0.4 (0.2-0.6) | 54/331 (16.3) | 15.6 | 16.1 (7.1-36.6) |
| Traditional healer | 5/31 (16.1) | 1.3 | 2.0 (0.7-5.7) | 5/32 (15.6) | 0.4 | 0.5 (0.2-1.4) | 8/29 (27.6) | 31.8 | 41.5 (13.3-129.3) |
| Other | 13/44 (22.8) | 1.9 | 2.3 (1.1-4.9) | 14/59 (23.7) | 0.7 | 0.8 (0.4-1.5) | 7/57 (12.3) | 9.9 | 10.6 (3.4-33.3) |
| Area | | | | | | | | | |
| Rural | 159/1016 (15.7) | 1 | 1 | 245/1023 (24.0) | 1 | 1 | 120/1002 (12.0) | 1 | 1 |
| Urban | 99/800 (12.4) | 0.8 | 1.0 (0.7-1.4) | 109/798 (13.7) | 0.5 | 0.7 (0.5-0.9) | 111/673 (14.2) | 1.2 | 1.6 (1.1-2.2) |
| Remote | 47/253 (18.6) | 1.3 | 1.6 (1.1-2.3) | 80/254 (31.5) | 1.5 | 1.2 (0.8-1.7) | 17/248 (6.9) | 0.5 | 1.4 (0.8-2.6) |
| Region | | | | | | | | | |
| South | 134/1302 (10.3) | 1 | 1 | 143/1305 (11.0) | 1 | 1 | 175/1280 (13.7) | 1 | 1 |
| North | 129/558 (23.1) | 2.6 | 3.8 (2.7-5.4) | 261/561 (46.5) | 7.4 | 4.9 (3.7-6.5) | 28/547 (5.1) | 0.3 | 1.0 (0.6-1.6) |
| Central | 42/209 (20.1) | 2.3 | 2.9 (1.9-4.4) | 20/209 (14.4) | 1.5 | 1.4 (0.9-2.2) | 45/207 (21.7) | 1.8 | 3.0 (1.9-4.8) |
| Total | 305/2069 (14.7) | | | 434/2075 (20.9) | | | 248/2034 (12.2) | | |

Long total delay: ≥12 weeks. Long patient delay: ≥6 weeks. Long HCP delay: ≥6 weeks. * Adjusted for variables of sex, age, initial visit, area and region in the model. OR: Odds ratio; aOR: adjusted odds ratio. 95% CI: 95% confident interval. HCP: Health care provider.

Mean patient delay was 4.7 weeks, with a median of 3 weeks (range: 1-48). Men reported earlier with TB symptoms than women (4.4 and 5.6 weeks respectively, $p<0.005$). Increasing age and increasing distance between the patient's home and the health care facility visited initially were associated with longer patient delay ($p<0.05$). Mean patient delay was longer for patients who initially visited public health facilities such as communal health posts (6.1 weeks), district health centers (5.9 weeks) or hospitals (4.5 weeks) than for patients who first visited traditional healers (3.9 weeks), private practitioners (3.3 weeks) or pharmacies (1.9 weeks) ($p<0.005$). Patients delays were also longer in remote (7.1 weeks) or rural settings compared to urban settings (5.3 weeks, $p<0.005$), and in the northern region (9.1 weeks, $p<0.005$).

Patient delay accounted for 63% of total delay overall. This proportion was lowest for patients who initially visited a pharmacy (21%) or a private practitioner (46%), or who lived in the central region (44%). The proportion of patient delay out of total delay was highest for patients who initially visited a district health center (89%) or public hospital (80%), patients who belonged to ethnic minorities (87%), and patients who lived in the northern region (81%) (Table 1).

Mean health care provider (HCP) delay was 2.8 weeks with a median of 1 week (range: 0-25). HCP delays were longer for women (2.9 weeks, $p<0.005$) and for patients aged 34-45 years (3.5 weeks) or 65 years or more (3.1 weeks). HCP delays were also longer for patients with a high level of education (3.2 weeks), or who visited initially the private sector ($p<0.001$), as well as for patients living at more than 5 km distance from the health facility ($p<0.005$), patients living in rural areas ($p<0.001$), and patients in the central region ($p<0.001$)

Long total delay was observed for 305 patients (15%, 95% CI 13%-16%), long patient delay for 434 (21%, 95% CI 19%-23%), and long HCP delay for 248 (12%, 95% CI 11%-14%). Of 1,731 patients with a total delay ≤12 weeks, 99 (6%) reported long HCP delay and 239 (14%) long patient delay ($p<0.001$). Of 303 patient with long total delay, 128 (42%) reported long HCP delay, 154 (51%) reported long patient delay, and 21 (7%) reported both ($p<0.001$). Thus, patient delay contributed most to long total delay.

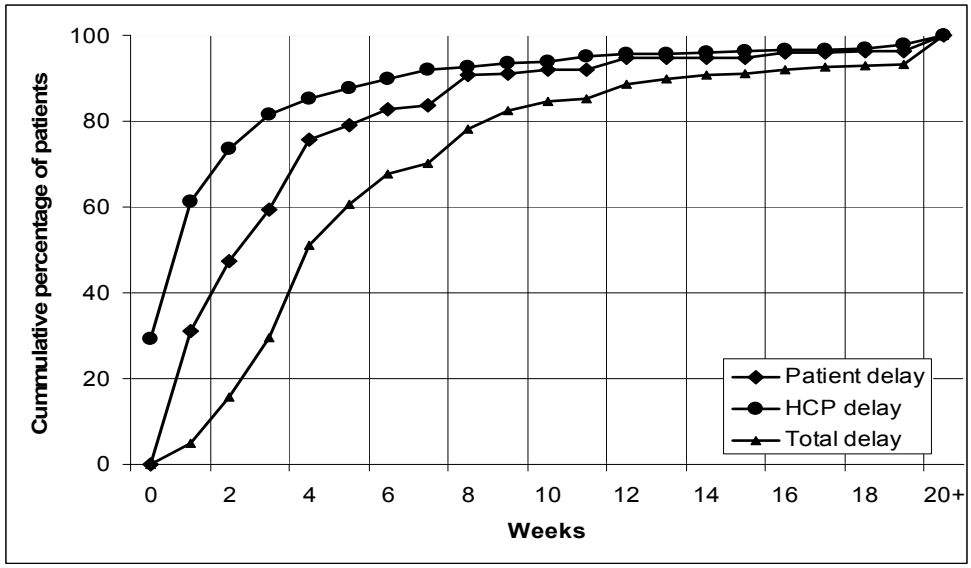
In a logistic regression model, long total delay was significantly associated with initial visit to a pharmacy (adjusted odds ratio, aOR 4.3) or a private practitioner (aOR 1.7). In addition, it was associated with middle age (aOR 1.8 for 34-44 years and aOR 2.1 for 44-54 years), with living in remote areas (aOR 1.6) and with living in the central or northern compared to the southern region (aOR 3.8 and aOR 2.9 respectively; Table 2).

The logistic regression models for long patient delay and HCP delay showed opposite associations with initial health care provider (Table 2). Long patient delay was more common among patients who initially visited a public provider, whereas long HCP delay was substantially more common among patients who initially visited a private provider. Compared to the district health center as the initial provider, the relative risks were 66 for pharmacy, 42 for traditional healer, and 16 for private practitioner. Other independent risk

factors for long patient delay were female sex, belonging to an ethnic minority, living at more than 5 km distance from the DTU, and residence in the northern region. Other independent risk factors for long HCP delay were living at more than 5 km distance from the DTU and residence in the central region (Table 2).

In each of the logistic regression models there was significant interaction related to the initial HCP. For total delay, this differed significantly by region. Compared to a public health facility as first provider, the risk of long total delay when the first provider was a pharmacy, private practitioner, traditional healer or other private provider was 3.9 times increased (OR 3.9, 95% CI 2.6-6.1) in the south and 2.8 times (OR 2.8, 95% CI 1.3-6.1) in the center, but only 1.2 times in the north (OR 1.2, 95% CI 0.7-2.3; likelihood ratio test for interaction: $p<0.01$). The risk of long patient delay if the first provider was private rather than public was reduced by half among men (OR 0.5, 95% CI 0.4-0.8), but to one third among women (OR 0.3, 95% CI 0.1-0.5; $p<0.05$). The risk of long HCP delay if the first provider was private rather than public was 10.5 times increased in rural districts (OR 10.5, 95% CI 5.9-18.6) and 16.8 times in urban districts (OR 16.8, 95% CI 9.0-31.7), but only 3.9 times in remote districts (OR 3.9, 95% CI 1.2-2.5; $p<0.05$).

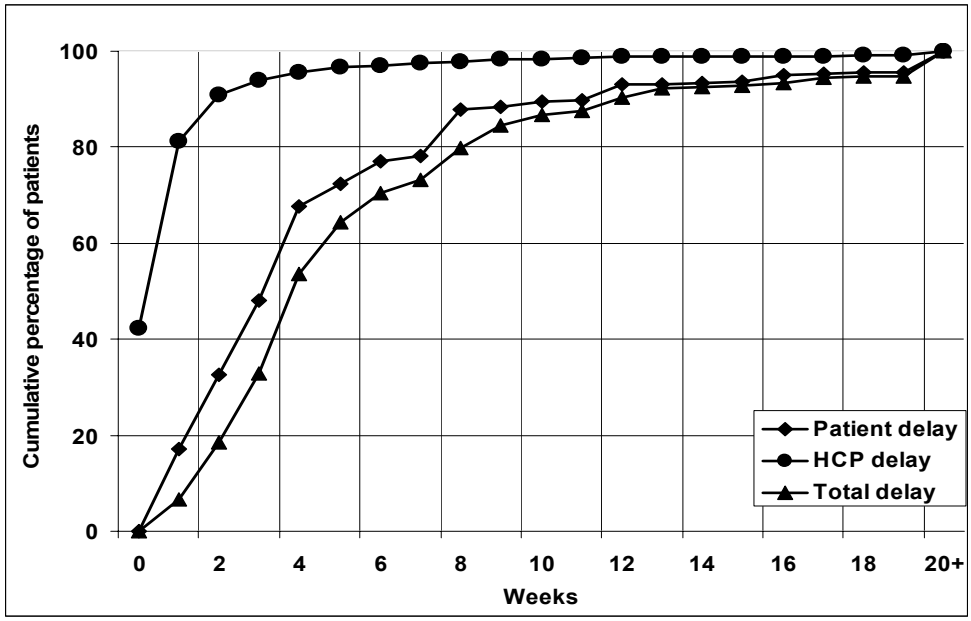
**Figure 1. Cumulative proportion of patient, health care provider and total delay among new smear-positive tuberculosis patients.**




The associations with initial provider were further analyzed by comparing the distribution of delay periods (Figures 1, 2 and 3). Eighty-eight percent of patients who initially visited a public provider had been detected and started treatment within 12 weeks, compared to 81%

of patients who initially visited a private provider ($p<0.001$). Of the patients who initially visited a public provider, 72% had reported with symptoms within 6 weeks of onset, compared to 92% of patients who initially visited a private provider ($p<0.001$). Within 6 weeks of the initial visit, 97% of patients had started TB treatment if the initial provider had been public, compared to 71% if the initial provider had been private ($p<0.001$). Overall, patients with long total delay accounted for 49% of the cumulative number of delay-weeks of all patients. This was 62% both for long patient and for long HCP delay.

**Figure 2. Cumulative proportion of patient, health care provider and total delay among new smear-positive tuberculosis patients who initially visited public health care providers.**

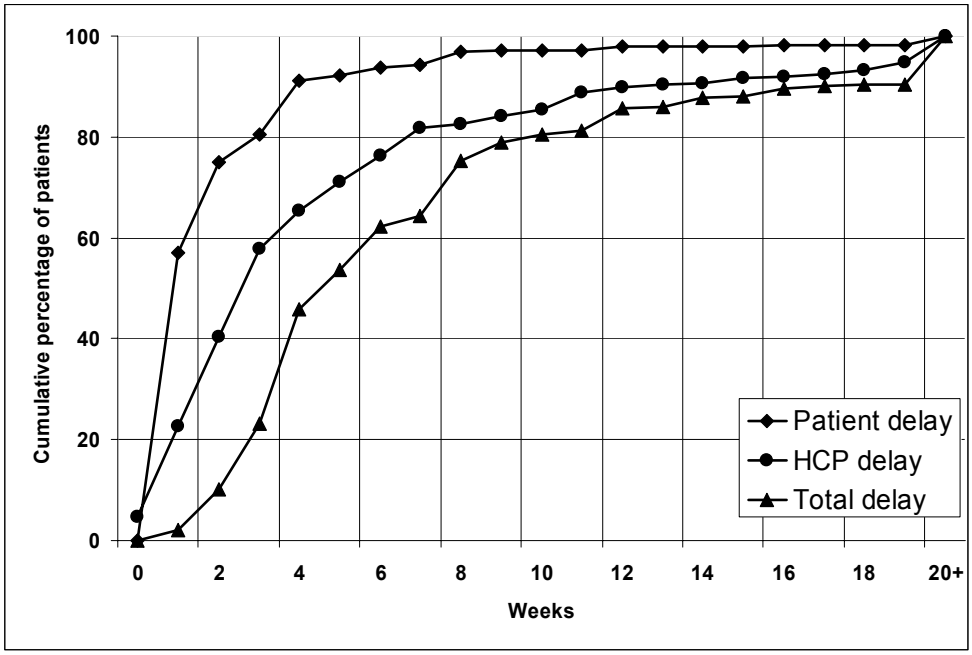



## DISCUSSION

This study showed an overall mean time from onset of cough to TB treatment for new smear-positive pulmonary TB patients in Vietnam of 7.5 weeks. This is almost half less than the delay reported from 4 provinces in Vietnam in 1996 (13.3 weeks) [12], and much lower than the delay reported from other high-prevalence countries such as Nepal [19], South Africa [20], Tanzania [2], Ethiopia [3,4] and Thailand [7], where it ranged from 9 to 23 weeks. Patient delay (on average 4.7 weeks) contributed more than HCP delay (on

average 2.8 weeks) to the total delay in our study. In 1996 mean patient delay was 5.8 weeks and mean HCP delay was 6.1 weeks [12]. Although the study in 1996 measured delay by onset of any TB symptom instead of just cough, and was not representative for Vietnam, the data suggest a decrease in total delay since 1996 that is primarily due to a decrease in HCP delay.

**Figure 3. Cumulative proportion of patient, health care provider and total delay among new smear-positive tuberculosis patients who initially visited private health care providers.**




The short delay found in our study may be explained by the development of the general health care and TB control network in Vietnam over the past years [21,22]. This may have impacted both on patient and on HCP delays. Access of the poor to basic health services has been improved by providing free health cards, user fee exemption, reimbursement of travel cost and other enablers [21,22]. Knowledge of commune health staff and volunteers at village level also has improved over the recent years. A community health network enhances detection and referral of patients who are suspect of having TB to the appropriate level for diagnosis [23]. Health information campaigns may have raised the awareness of the community about TB symptoms and the need for timely diagnosis [23].

We found clear associations between delay and the type of health care provider first visited by the patient because of cough. Long patient delays were most frequent if this had been the district health centre, and least frequent if this had been a private provider. Long HCP delays were however more frequent among patients who visited a private provider first, as were long total delays. These findings are in accordance with data from Ho Chi Minh City, where, compared to public providers, relative risks for long HCP delay were 5.5 for private pharmacies as the first provider, and 2.1 for private physicians as the first provider [13]. Thus, although initial visits to private health services tended to be earlier after the onset of cough than initial visits to public health services, the time until diagnosis of TB tended to be longer, to the net effect of longer delays if the initial provider had been private. This suggests that referral from the private sector is an important problem. One-third of all patients in our study had initially visited a private provider, although this proportion was higher in the southern (44%) and central (37%) than in the northern region (8%). Also, the observed interaction indicates that referral from private providers is less of a problem in the north and in remote settings. Education on diagnosis of TB of private health care providers and pharmacies may help prevent long health care provider delays, as may implementation of public-private mix DOTS projects in urban and rural areas, in particular in the southern and central regions. The growth of the private sector in Vietnam and its impact on diagnostic delay warrant regular monitoring of these delays.

The 21% of patients who had patient delays of more than 6 weeks accounted for 61% of the cumulative patient delay period, and the 13% of patients who had HCP delay of more than 6 weeks accounted for 62% of the cumulative HCP delay. It supports our hypothesis that efforts should not be put in further reduction of total median delay, but in prevention of long delays, since they contribute most to the cumulative delay of all patients and thereby to transmission.

The sex difference in delay is small and similar to the difference found by previous studies [12,14,15,24-26]. These longer delays among women, as well as the low proportion of women among patients in this study and among notified TB patients in Vietnam in general, may indicate lower access to diagnosis and treatment of TB for women compared to men [12,25,26]. However, biological differences between men and women with respect to TB incidence and sensitivity of smear examination may play a role as well [24,27]. Analysis of model interactions suggests that, although women tend to report with cough to private providers earlier than men, this does not result in shorter overall delays, supporting earlier findings that health care providers visited by women tend to be less qualified [24,25]. These analyses showed other risk factors for long delay that may help target interventions, such as belonging to an ethnic minority, living in particular geographic areas, middle age and female sex.

There were several limitations to our study. First, the reported duration of symptoms is based on the patients' recall and interpretation. Recall bias is thus a serious threat to the estimates of delay and actions taken. Unfortunately there is no feasible method which can deal with this problem. Second, selection of patients might be biased. Some patients diagnosed within the NTP may have been referred to other facilities or have sought

treatment in the private sector before they were registered. These patients were not included in our study. Third, both health workers and patients can contribute to long HCP delay: patients can delay the start of treatment as well as the health worker, e.g. for fear of stigmatization or reluctance to tell employers [28]. Finally, the observed association of long delay with private health care provider does not necessarily imply causation. Patients may have been more "at risk" of visiting a private practitioner simply because more time elapsed between onset of symptoms and diagnosis at the TB unit.

## CONCLUSIONS

On average, total, patient and health care provider delays were short in this nation-wide study of TB patients in Vietnam. Nonetheless, 15% of patients reported total delays ≥12 weeks, and accounted for half of the cumulative number of delay-weeks. Initial visit to the private sector had a considerable impact on the length of delays but with distinct regional differences across the country. Efforts should be made to further reduce diagnostic delays by improving the referral from the private to the public health sector.

## ACKNOWLEDGEMENTS

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# Chapter 4

# Evaluation of sputum smear microscopy in the National Tuberculosis Control Programme in the north of Vietnam

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**ABSTRACT**

*Objective:* To assess the yield of sputum smear microscopy and sex differences in the National Tuberculosis Control Programme in the north of Vietnam.

*Methods:* Review of registers of 30 randomly selected laboratories (26 districts, 4 provincial level).

*Results:* The average daily workload per technician was 4.4 examinations in district and 5.3 examinations in provincial laboratories. To find one smear-positive case, 9.7 suspects were examined and 29.3 smears done. The smear-positive rate (mean 10.3%) was higher among men (11.6%) than among women (8.4%, $p<0.001$). There were more men than women among tuberculosis (TB) suspects (male:female ratio 1.36, 95%CI 1.19–1.54), but even more so among smear-positive patients (1.89, 95%CI 1.64–2.14), irrespective of specimen quality and number of smears examined. Three smears were examined for 18 055 suspects (61.7%). The incremental gain was 33.5% and 4.9% for the second and third smear examination, respectively; 186 (95%CI 160–221) smears needed to be examined to find one additional case of TB with a third serial examination.

*Conclusion:* The diagnostic process seemed generally efficient. The male:female ratios suggest higher TB incidence in men rather than lower access to TB facilities for women. The third smear examination could be omitted.

## INSTRODUCTION

Tuberculosis (TB) remains a major public health problem in Vietnam [1,2]. Sputum smear examination by microscopy for acid-fast bacilli is a key method of TB case finding in developing countries. Since 1986, the National Tuberculosis Control Programme (NTP) has implemented a standard recording and reporting system for smear examination, as recommended by the International Union Against Tuberculosis and Lung Disease (The Union) [3]. This is based on laboratory registers to record the results of every TB examinee at district microscopy centres. Examination of three sputum specimens, of which the first and third are collected on the spot and the second early in the morning (spot-morning-spot), is recommended to exclude smear-positive pulmonary TB. The results are entered in three separate columns on the same line. Sputum smear examination is free of charge.

In Vietnam, there are 627 peripheral laboratories capable of performing smear microscopy at district health centres. The population per laboratory varies by region, and is about 125 000 on average. The district laboratories are supported with quality assurance by 61 intermediate-level provincial laboratories.

In this study, we assessed the workload of laboratory staff, and the use and yield of sputum smear examination in relation to the demographic characteristics of TB suspects and cases under routine NTP conditions in the north of Vietnam. To assess access to diagnostic services, we were particularly interested in variations by age and sex. In addition, we evaluated the number of slides that needed to be examined to find one additional case of TB with a second and third serial diagnostic sputum smear examination.

## METHODS

*Study population and sampling*

Thirty microscopy centres were selected randomly by cluster sampling with probability proportional to the number of smear-positive TB cases notified in 1997. Eligible for selection were all centres that performed sputum smear examination by the Ziehl-Neelsen method.

Laboratory staff were interviewed using a structured questionnaire to obtain data on numbers of TB laboratory technicians, working days, microscopes available, smears done (diagnosis and follow-up smears), suspects examined and smear-positive cases detected in 1998.

In addition, laboratory record data were collected of all TB suspects (defined as any person presenting at the laboratory with a history of cough of $\geq$2 weeks) examined in 1998, including sex, age and reason for examination, sputum appearance and results of smear examination. In accordance with NTP guidelines, a TB case was defined as a suspect with at least two positive sputum smear examinations or one positive sputum smear examination with an abnormal chest x-ray (CXR) or positive culture examination.

*Data management and analysis*

Data were entered in Epi Info v6.4 (Centers for Disease Control and Prevention, Atlanta, GA, USA). A 10% random sample of the laboratory record data was re-entered for data validation and showed only minimal errors. Data were analyzed in STATA v8 (Stata Corp, College Station, TX, USA). Comparison of the proportions of positive smears and of male examinees calculated directly from the total data set with the averages over the laboratory-specific proportions showed no significant differences. We therefore assumed a self-weighted sample and calculated proportions over all laboratories combined [4]. Confidence intervals (CI) and *P* values were adjusted for the cluster design by first-order Taylor linearization and the second-order correction of Rao and Scott of the Pearson $x^2$ test, respectively, as implemented in the STATA 'svy' commands [5,6].

We calculated the number of smears required to identify one additional case of TB with a second or third sequential smear examination, as described by Rieder et al [7]. This number depends on the proportion of cases among suspects and the incremental gain from the first to the second and from the second to the third examination, respectively. The incremental gain is defined as the proportion of all TB cases diagnosed by the second or third smear examination if previous examinations were negative [8]. The product of these two proportions provides the overall fraction of the suspect population that are positive for the first time on the second or third serial examination. The reciprocal value of this proportion provides the number of smears required to identify one additional case; a Bayesian 95%CI is obtained by the Markov Chain Monte Carlo approach [7].

This method underestimates the incremental gain if not all suspects had a complete set of three examinations. We adjusted for this by assuming that the probability of a positive smear did not depend on whether the examination had actually been done. The published algorithm was used to impute the number of missed cases by failing to examine an entire set of three examinations for each suspect [7]. This number was used to estimate the *potential* incremental gain, i.e., the proportion of all TB cases diagnosed by the second or third smear examination if previous examinations were negative and three smear examinations had been done for all suspects.

**RESULTS**

Of the 30 selected laboratories, 26 were district (average population 170 000; range 52200–270 000) and four provincial centres (1 723 000; 881 000–3 580 000). Five were in remote, mountainous areas (68 200; 60 000–80 000) with generally long distances and poor transport services. All used the standard NTP laboratory register.

Of 107 860 smears, 49% were performed at district laboratories and 83% were diagnostic (Table 1). The proportion of diagnostic smears was larger in district (86%) than in provincial laboratories (79%). The average number of smears performed by one laboratory was higher in provincial (22.3 smears/laboratory/day) than in district laboratories (5.0

smears/laboratory/day), but the average number of smears performed by one technician was not very different: 4.4 and 5.3 smears/technician/day, respectively. For each smear positive case detected, 29 diagnostic smears had been examined on average. This number was higher in the provincial (46) than in the district (22) centres.

**Table 1. Workload of 30 smear microscopy laboratories in the northern part of Vietnam, 1998.**

| | Total<br>n | District<br>n | Province<br>n |
|---|---|---|---|
| Laboratories | 30 | 26 | 4 |
| Smears | 107,860 | 52,468 | 55,392 |
| Diagnostic smears | 88,973 | 45,362 | 43,611 |
| Follow-up smears | 18,947 | 7,166 | 11,781 |
| Work load of laboratories (smears per day) (*) | 6.4 (2.5-13.0) | 5 (2.5-9.8) | 22.3 (13.9-75.9) |
| Work load of TB technician (*) | 4.5 (2.5-8.5) | 4.4 (2.4-8.5) | 5.3 (3.1-13.9) |
| Suspects | 29,639 | 20,065 | 9,574 |
| Positive cases | 3,040 | 2,099 | 941 |
| Suspects examined per positive case (†) | 9.7 | 9.6 | 10.2 |
| Smears examined per positive case (†) | 29.3 | 21.6 | 46.3 |

* Median (25 –75 percentile)
† Mean

Of 29 639 suspects whose laboratory records were included, 20 065 (68%) had been examined by district laboratories. Information about sex and age was available for 29 243 (99%); 16 877 (58%) were male (Table 2). The average number of suspects examined per positive case was 9.7, with limited difference between district (9.6) and provincial (10.2) laboratories. The median number of smears examined per positive case was 23.1 and was identical among district and provincial laboratories.

Men were more likely to present for sputum smear examination than women: the overall male:female ratio among suspects was 1.36 (95%CI 1.19–1.54), compared to 0.97 in the general population. This was observed for all age groups except for those aged 0–14 years and 25–34 years. Men were also more likely to be diagnosed with smear-positive TB (overall male:female ratio among cases 1.89), compared both to the general population and

**Table 2. TB suspects, smear-positive TB cases, and male:female ratios by age group.**

| | Cases/suspects | | | Male:female ratio | | | |
|---|---|---|---|---|---|---|---|
| Age, years | All* n/n (%) | Males* n/n (%) | Females* n/n (%) | General population ratio | TB suspects ratio (95% CI) | TB cases ratio (95% CI) | OR (95% CI)* |
| 0-14 | 6/445 (1.3) | 3/237 (1.3) | 3/208 (1.4) | 1.08 | 1.14 (0.96-1.32) | 1.00 (0.39-2.39) | 0.88 (0.21-3.71) |
| 15-24 | 134/1484 (9.0) | 81/881 (9.2) | 53/603 (8.8) | 0.98 | 1.46 (1.13-1.79) | 1.53 (1.06-2.00) | 1.05 (0.77-1.44) |
| 25-34 | 342/3191 (10.7) | 233/1780 (13.1) | 109/1411 (7.7) | 0.99 | 1.26 (0.95-1.57) | 2.14 (1.72-2.55) | 1.80 (1.32-2.45) |
| 35-44 | 574/5133 (11.2) | 426/2819 (15.1) | 148/2314 (6.4) | 0.93 | 1.22 (1.00-1.44) | 2.88 (2.17-3.59) | 2.61 (2.15-3.15) |
| 45-54 | 473/5057 (9.4) | 323/2857 (11.3) | 150/2200 (6.8) | 0.87 | 1.30 (1.09-1.51) | 2.15 (1.61-2.69) | 1.74 (1.37-2.21) |
| 55-64 | 581/6254 (9.3) | 369/3652 (10.1) | 212/2602 (8.2) | 0.78 | 1.40 (1.22-1.58) | 1.74 (1.43-2.05) | 1.25 (1.05-1.53) |
| 65+ | 888/7646 (11.6) | 525/4633 (11.3) | 363/3013 (12.1) | 0.68 | 1.54 (1.37-1.70) | 1.45 (1.18-1.71) | 0.93 (0.75-1.16) |
| Total | 3002/29243 (10.3) | 1964/16877 (11.6) | 1038/12366 (8.4) | 0.97 | 1.36 (1.19-1.54) | 1.89 (1.64-2.14) | 1.44 (1.26-1.63) |

* p-value for difference across age categories <0.001.
TB = tuberculosis; CI: confidence interval; OR: odds ratio of male suspects compared to female suspects for being a smear-positive TB case.

**Table 3. Numbers of TB suspects and smear-positive cases, and proportion smear-positive, by number of smears examined and sex.**

| smears examined n | TB suspects* | | | Smear-positive cases† | | | Proportion smear-positive per 100 tuberculosis suspects‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total n (%) | Male n (%) | Female n (%) | Total n (%) | Male n (%) | Female n (%) | Total (95% CI) | Male (95% CI) | Female (95% CI) |
| One smear | 4974 (17.0) | 3091 (18.3) | 1883 (15.2) | 154 (5.1) | 113 (5.8 ) | 41 (3.9) | 3.1 (2.1-4.1) | 3.7 (2.7-4.6) | 2.2 (0.9-3.4) |
| Two smears | 6214 (21.2) | 3397 (20.1) | 2817 (22.8) | 635 (21.2) | 393 (20.0) | 242 (23.3) | 10.2 (6.5-14.0) | 11.6 (7.3-15.8) | 8.6 (4.9-12.3) |
| Three smears | 18055 (61.7) | 10389 (61.6) | 7666 (62.0) | 2213 (73.7) | 1458 (74.2) | 755 (72.7) | 12.3 (9.7-14.8) | 14.0 (11.1-17.0) | 9.8 (7.9-11.8) |
| Total | 29243 (100) | 16877 (100) | 12366 (100) | 3002 (100) | 1964 (100) | 1038 (100) | 10.3 (9.0-11.6) | 11.6 (10.1-13.1) | 8.4 (7.1-9.6) |

* Difference between male and female suspects: p=0.009.
† Difference between male and female cases: p=0.018.
‡ Difference in proportion positive between male and female suspects with 3 smears examined: p<0.001.

to suspects, with the exception of the youngest age group. The male:female ratio among cases peaked in the age group 25–54 years (Table 2).

The proportion of cases among suspects was higher among men (11.6%) than among women (8.4%, odds ratio [OR] 1.44, p<0.001). There was a distinct age pattern in this sex difference. In the age groups 25–54 years, men were pproximately twice as likely to be smear-positive as women (p<0.001), whereas there were no sex differences in the youngest (0–24 years) and oldest (>65 years) age groups.

Sixty-two per cent of subjects had three smears examined (Table 3); 21% had two and 17% only one. Women had two or three smears examined slightly more often than men (p= 0.009).

The overall proportion smear-positive among the suspects was 10.3%. This proportion decreased from 12.3% among suspects with three to 10.2% among suspects with two and 3.1% among suspects with only one smear examined. The number of smears examined did not affect the sex difference in the proportion who were smear-positive (Table 3).

The proportion smear-positive was higher with the morning (second) specimen (10.8%), than with each of the spot specimens: 6.8% for the first and 9.5% for the third (p<0.001, Table 4). This pattern was similar among men and women; the sex difference in the proportion positive was independent of the timing of specimen collection. The third sputum smear was more likely to be omitted than the second or the first.

**Table 4. Proportion of smear examination positive, by sequence of specimen and sex**

| Sputum specimen | Positive smears/smears performed | | | |
|---|---|---|---|---|
| | Total n/N (%) | Males n/N (%) | Females n/N (%) | P-value* |
| First (on spot) | 1887/27806 (6.8) | 1257/16055 (7.8) | 630/11751 (5.4) | <0.001 |
| Second (morning) | 2634/24492 (10.8) | 1706/13911 (12.3) | 928/10581 (8.8) | <0.001 |
| Third (on spot) | 1811/18974 (9.5) | 1210/10910 (11.1) | 601/8064 (7.5) | <0.001 |
| Total | 6332/71272 (8.9) | 4173/40876 (10.2) | 2159/30396 (7.1) | <0.001 |
| P-value† | <0.001 | <0.001 | <0.001 | |

* P-value for difference between male and female tuberculosis suspects
† P-value for difference between first, second and third specimen.

Information on macroscopic appearance was available for 69 534/71 567 sputum specimens (97%); 30 266 (42%) contained saliva. The proportion positive was 8.8% among all specimens, 14% among mucoid, purulent or blood-stained specimens and 2.1% among salivary specimens (p≤0.001). Among men, these proportions were 16% and 2.4%, respectively, compared with 12% and 1.6% among female suspects, respectively (p for sex difference 0.004). The proportion positive at grades 2+ or 3+ was higher among mucoid, purulent or blood-stained (3.2%) than among salivary specimens (0.4%, p<0.001).

The estimated number of TB cases missed by not performing the complete set of three smear examinations was 241, i.e., 8% of 3097 expected cases (Table 5). The potential incremental gain of performing a second and third smear examination was 34% and 4.9%, respectively. The estimated number of smears needed to be examined to find one additional case of TB was 27 for the second and 186 for the third smear (Table 5).

**Table 5. Estimated number of smear-positive cases missed, potential incremental gain from serial smears, and number of slides needed to be examined to identify one additional case with each serial sputum smear examination.**

| | Cases missed* n | Potential incremental gain % | Smears needed to be examined to identify one additional case n (95% CI) |
|---|---|---|---|
| 1st examination | | 61.6 | 15 (14-16) |
| 2nd examination | 185 | 33.5 | 27 (26-29) |
| 3rd examination | 56 | 4.9 | 186 (160-221) |

* Estimated number of smear-positive cases missed by not completing a series of three examinations. See reference 7 for calculation.
CI = confidence interval.

## DISCUSSION

In this part of Vietnam, the NTP has a well developed laboratory registration system following Union recommendations [3].

The workload ranged between 2.5 and 8.5 smears per day per laboratory technician. This was less than is generally considered as the capacity of a laboratory technician (20–25 smears) [9,10]. A similar study in several high-incidence countries found an average number of smears performed per working day of 6.0, ranging from 4.0 in Nicaragua to 19.3 in Malawi [11]. It may therefore be concluded that the laboratory network could accept more examinations. However, at the district level, the TB laboratory is integrated with the general laboratory, and sputum smear examination represents only part of the daily duties of the laboratory technicians.

The proportion smear-positive among suspects was 10.3%. According to Union recommendations, this reflects a fairly good screening process of TB suspects and adequate technical procedures for microscopy in the NTP, and indicates acceptable efficiency of smear microscopy [12]. Although higher than in Nicaragua (5%), the proportion positive was lower than in Tanzania (19%), Malawi (17%), Senegal (19%) and Benin (32%) [8,11]. In these countries, CXRs may play a more important role in screening, and patients may seek a diagnosis at a later stage of the disease, with a consequently high bacillary load.

The proportion positive is an important indicator for estimation of supplies. The Union recommendation for the calculation of laboratory supplies has been that 10 suspects need to be examined with three smears each to identify one case of sputum smear-positive TB [12]. We found that 29 smears were indeed examined per case on average, although this was lower at the district centres (22). The higher number of smears at the provincial centres (46) reflects a relatively high case load of referred smear-negative suspects who, as part of the diagnostic work-up, have up to six smears examined.

The observed male:female ratio of smear-positive patients (1.9:1) was in accordance with that reported globally (2:1) or among notified TB cases in Vietnam in 1998 (2:1) (NTP, unpublished data) [1]. The causes of this sex difference in case notification are not well understood [13–15]. We found that, compared to women, men were more likely to present for smear examination, but also to be smear-positive upon examination. In the age group 25–54 years, the smear-positive rate was approximately two times higher for men than for women, suggesting that the sex difference reflects biological phenomena rather than lower access to TB diagnosis for women. These may include not only true differences in TB incidence, but also differences in the bacillary load of sputum specimens and thereby in the sensitivity of smear examination [16,17]. Differences in the quality or number of specimens is a less likely explanation, as the sex difference remained after stratification for specimen appearance, timing of collection and number of smears examined.

The 1.4:1 male:female ratio for TB suspects may nevertheless reflect gender-related barriers in the access to TB services, as suggested by other research and anecdotal evidence [17–19]. Such barriers may be related to cultural beliefs, traditional customs and practices, labour division within the household and seasonal work preventing women from being diagnosed in time and treated properly [18,19]. Also, the stigma related to TB tends to be greater for women than for men.

The Vietnamese NTP has implemented the recommendation to obtain three sputum smears, the first on the spot, the second in the early morning, and the third again on the spot when the second is delivered [3]. Compliance with this policy was low (62%). However, 95% of the smear-positive patients were detected by the first two smears, i.e., the third smear yielded only 5% additional cases. This yield was somewhat higher than in Ethiopia (1%) and Bangladesh (3%), but similar to that in Tanzania (4%) [8,20,21] although in the latter study the potential incremental gain of the second smear was considerably higher.

Rieder et al. recently presented a method to objectively assess the appropriateness of current recommendations with regard to the numbers of smears to be examined in different settings [7]. We applied this to the north of Vietnam, and estimated that 186 smears needed to be examined to detect one additional TB case by a third smear examination. This is at the upper end of what experts would consider an efficient use of human and other resources [7]. Omitting the third sputum specimen might thus be an option for the Vietnamese NTP, although further studies need to clarify whether this should apply to the whole country. It has limited impact on case finding, while it saves work for the health services and limits the burden to TB suspects. On the other hand, the TB laboratory workload in the north of

Vietnam is already limited. The advantages should thus be carefully weighed against the disadvantage of detecting fewer cases.

The morning specimen had a higher yield than the spot specimens, probably reflecting higher bacillary load. Macroscopic inspection indicated that almost half of the specimens were predominantly salivary. Further studies are needed on how the technique of sputum collection can be improved.

This study has limitations. The routine laboratory registers may have contained errors. Furthermore, referral of TB patients between provincial microscopy centres and district TB units was not taken into account and may have introduced bias in the age and sex distribution of suspects and TB cases. Finally, the assumption underlying the estimation of the potential incremental gain of the third sputum smear, i.e., that missed examinations had the same probability of a positive result as performed examinations, may not entirely hold. We observed a significantly higher yield of the third than of the first specimen, although both were collected on the spot. This suggests that suspects who provided a third specimen had a higher than average probability of being smear-positive, e.g., because their symptoms raised higher suspicion of TB than those of suspects who missed the third specimen. If this is true, we have overestimated the potential incremental yield of the third examination and under–estimated the number of smears needed to be examined to detect one additional case. This would reinforce the notion that the third smear examination could be omitted in the diagnostic process.

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# Chapter 5

# Variation in case notification of tuberculosis: Disentangling incidence and access to care

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**ABSTRACT**

*Setting:* All communes and districts in Vietnam.

*Objective:* To assess to what extent the variation in tuberculosis (TB) notification is explained by variation in TB incidence and by variation in access to diagnosis and treatment.

*Design:* Cross-sectional survey of all districts and communes in the NTP surveillance system. Retrospective reviews of all district TB laboratory registers for the second quarter of 2003.

*Results:* The overall annual notification rate of smear positive TB per 100 000 population was 78 (95% CI 77-79); 9 per 1000 population had sputum smear examination (suspect rate; 95% CI 9-9). Notification and suspect rates were lowest in the communes in the Red River Delta (46.8/100 000 and 4.1/1000 respectively) and highest in those in the North East Highland (117.2/100 000 and 18.2/1000 respectively), both in the northern region of the country. Notification rates and the suspect rates were significantly associated with most of the demographic indicators and TB control indicators analyzed. In the multivariate analyses, both notification and suspect rates were significantly associated with zone, urbanity and indicators of TB control and showed no relevant association with ethnic composition or poverty status of the commune. In addition, case notification rates followed a north-south gradient. The distance to the district health center and availability of health care staff and microscopy centers were strong determinants of the suspect rate.

*Conclusion:* This study suggests that geographic variations in CNRs in Vietnam reflect both differences in access to care and epidemiological differences in TB distribution. The TB suspect rate is probably a useful summary indicator of the diagnostic effort that may be used to disentangle variations in TB incidence from variation in access to diagnosis.

## INTRODUCTION

For tuberculosis (TB) control, the World Health Organization (WHO) recommends the directly observed therapy short-course (DOTS) strategy (currently Stop TB Strategy) [1], and has set global targets for case detection and treatment success [2-5]. This strategy is considered one of the most cost-effective of all health interventions [6]. Successful TB control requires widespread access to diagnosis and care as well as proper case management. National Tuberculosis Control Programmes (NTP) therefore need knowledge of the epidemiology of TB in the country and of determinants of access to diagnosis and treatment. Analyses of TB case notification rates, which are routinely collected by such programmes, may provide useful information and allow monitoring of trends over time. However, TB case notification in high prevalence countries generally reflects not only incidence but also access, or from the perspective of a TB programme, case finding effort [7]. Variations in incidence of TB can thus be obscured by variations in case finding, and vice versa. For example, geographical gradients, urban-rural differences, and variations in socio-economic status may affect both incidence and access. One way of disentangling these two factors may be to use a single indicator that quantifies case finding efforts. A summary indicator that has been proposed is the TB suspect (or examination) rate, i.e. the proportion of the population examined by sputum smear microscopy over a defined period of time [8]. The suspect rate can be obtained relatively easily from TB laboratory registers and population data.

Vietnam is one of the seven countries with a high burden of TB in the Western Pacific region. It also ranks 13th on the list of the 22 high TB burden countries in the world [9]. Vietnam started to implement the DOTS strategy in 1989 and has exceeded the targets for case detection and treatment success since 1997 [10].

The TB control network is organized along a four-tiered pyramid: national, province, district and commune/village. The district tuberculosis unit (DTU) is responsible for confirmation of the diagnosis by microscopic sputum examination at the district general laboratory, initiation of ambulatory treatment to be provided near the patient's home, supervision of the conduct of the NTP in the communes, and integration with other health activities. At the base of the health care system is the commune health post (CHP), serving on average of 7,000-8,000 population. One commune health worker is responsible for communicable diseases including tuberculosis. Their tasks include identification and referral of suspects to the DTU, and application and supervision of ambulatory treatment.

Although all districts and communes in Vietnam provide DOTS services, they probably differ in the amount of effort they put into TB case finding and in access to TB diagnosis and treatment. This may be associated with poverty, remoteness and composition of the population. It is unclear to what extent such differences explain the marked variation in tuberculosis case notification rates (CNR) in Vietnam. The CNR are nearly 2 times higher in the south (96 new smear positive cases/100.000) than in the north (51/100.000) of the country [NTP, unpublished data]. By analyzing notification rates of smear-positive TB in Vietnam by individual commune during one quarter in 2003 we aimed to assess to what

extent the variation in TB notification is explained by variation in epidemiology and by variation in access to diagnosis, respectively.

**METHODS**

A cross-sectional study was conducted all 639 districts covering 10,659 communes in Vietnam, using data on TB suspects and cases for each commune from retrospective reviews of all district TB laboratory registers in the second quarter (1 April through 30 June) of 2003.

Data on demographic indicators (including urban/rural status and ethnic composition) as well as TB control indicators (including number of health care staff and TB staff in the commune, number of microscopy centres in the district, availability of X-ray services and user fees for smear examination) were collected from districts and communes by standard data collection forms. District TB coordinators were trained to collect the data from district TB and laboratory registers and fill in the forms.

Communes were defined as poor or non-poor based on government classification [11]. Region was defined as north, centre and south, and zone as the geographical and social-economical areas of the country, based on administrative boundaries. For the purpose of this study, a TB suspect was defined as any person who submitted at least one sputum specimen at the laboratory. A TB case was defined as any TB suspect with at least one positive smear examination as recorded in the district laboratory register.

Active case finding means that the health service actively identifies patient suspect of TB in the community, whereas in passive case finding the health service only acts when a patient reports with symptoms suspect of TB.

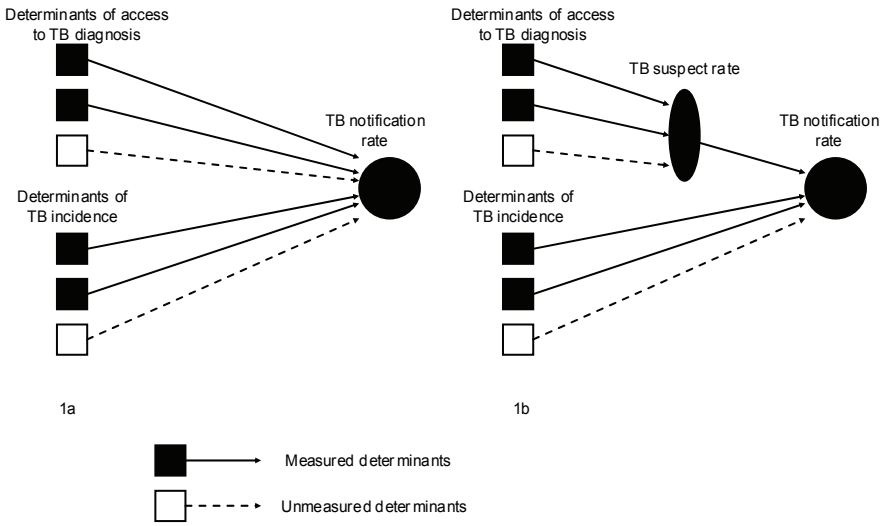
The annual TB suspect and case notification rates were estimated as the numbers of suspects and TB cases, respectively, divided by the commune population and then multiplied by 4 (to obtain suspect-years or patient-years).

Data were checked for completeness and quality before entry and corrected when necessary by referring back to the original records. Statistical analysis was performed using Stata SE v8 (Stata Corp., College Station TX, USA).

The analyses were based on the following reasoning. The TB case notification rate reflects TB incidence and the proportion of incident cases that are diagnosed by the NTP, and is thus associated with measured and unmeasured determinants of TB incidence as well as with measured and unmeasured determinants of access to diagnosis (figure 1a). For any unit (e.g. district, commune) the proportion of incident cases that are diagnosed is unkown, but can be assumed to correlate with the proportion of the unit population that has sputum smear examination, i.e. with the TB suspect rate. If true, associations between notification rates and variables among units that have equal suspect rates should reflect associations with TB incidence. By extension, determinants of TB incidence can be identified by a

multivariable unit-based analysis of case notification rates if it adjusts for differences in suspect rate (figure 1b). Conversely, variations in suspect rate between units can be analyzed to examine variations in case finding efforts. With our data, the extent to which the suspect rate correlates with the proportion of incident cases that is notified cannot be quantified directly. That proportion is likely to be associated with indicators of access to diagnosis, such as distance to the diagnostic unit, number of health care staff and whether examination fees are required. As a consequence, the suspect rate can be considered to be an intermediary factor in the associations between the case notification rate and these indicators, and to have a confounding effect on these associations (figure 1b) [12] An indirect assessment of the correlation between the suspect rate and the proportion of incident cases that are notified can therefore be obtained by comparing, in a multivariable analysis of case notification rates, the relative risks for these indicators before and after adjustment for suspect rate.

**Figure 1. TB suspect, notification rates and determinants of access to TB diagnosis: without (1a) and with (1b) adjustment for differences in suspect rate.**




Multivariable analyses of determinants of case notification and suspect rates were done using Poisson regression, taking the commune as the unit of analysis. In the models of case notification rates, suspect rates were checked for linearity by fitting them as deciles, and when linearity was observed, fitted as continuous variables. These models were estimated

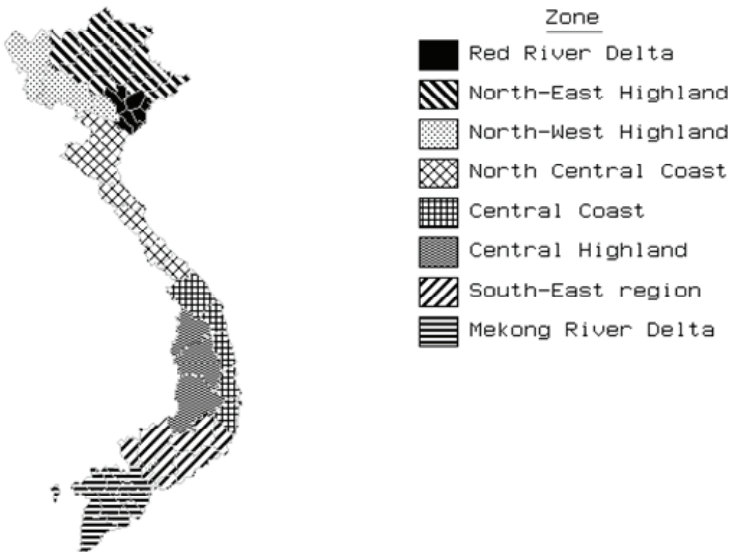
with and without suspect rate as an independent variable, and the validity of suspect rate as an indicator of diagnostic effort was assessed by comparing adjusted rate ratios for co-variates that were considered to reflect the health care response to TB. Since the numbers of communes in the analyses were very large, significant interactions were expected between many variables. We therefore only reported interactions with relevant sizes, defined as a more than 2-fold departure from the incidence risk ratio in the basic model.
Since suspects include patients finally diagnosed with TB, we repeated all analysis after replacing the suspect rate by the rate of suspects who remained smear-negative.

Significance testing was by the likelihood ratio chi-square test for comparing the likelihood of the model with, and without the variable or interaction term of interest.

**RESULTS**

Complete data were available for 10,286 (97%) of 10,659 communes. These belonged to 612 (96%) of the 639 districts in Vietnam. Table 1 summarizes the characteristics of these communes. The median commune population was 6,351 (IQR 3,914-9,664). Four-hundred seventy eight (5%) communes did not identify any TB suspect and 4,398 communes (43%) did not detect any TB patient during the study quarter.

**Figure 2. Map of Vietnam with 8 geographical zones**



The overall annual notification rate of smear-positive TB was 78 per 100,000 population (95% CI 77-79, Table 1). Notification rates ranged from 70/100,000 (95% CI 68-72) in the north to 78/100,000 (75-82) in the central and 87/100,000 (85-89) in the south of the country (data now shown, Figure 2).

The median suspect rate was 2.7 per 1,000 population and ranged across the communes from 0 to 109/1,000. Notification rates increased with increasing suspect rates from 16/100,000 among communes with suspect rates of less than 0.5/1,000, to 204/100,000 among communes with suspect rates of equal or more than 5 per 1,000 population.

Notification rates were significantly associated with most of the demographic and TB control indicators analyzed (Table 1). Tuberculosis notification was higher ($p<0.001$) in communes with ethnic minority groups, in poor communes, in non-urban communes, in communes applying a combination of passive and active case finding and in communes belonging to districts that did not ask fees for smear examination or had X-ray facilities. Notification rates increased with increasing number of microscopy centres in the district, and decreased with increasing numbers of population per commune health care staff and with distance from the commune health post to the district tuberculosis unit.

The multivariate analysis of the notification rate (Table 1) was based on 8,570 (83%) of 10,286 communes for which data on all included variables were available. In the multivariate model, there was no association between notification rate and ethnicity or poverty. Notification rates were significantly associated with zone, urban setting and with indicators of TB control (Table 2, model 1). Compared to the communes located less than 5 km from the DTU, the case notification rate was 0.65 times lower in communes located at more than 15 km distance. The CNR was 0.69 times lower when the district had no X-ray facilities. Communes that applied both passive and active case finding had 1.40 times higher CNR compared to those that applied passive case-finding only. Time since implementation of DOTS was significantly associated with the CNR but with no clear pattern (data not shown)

When the suspect rate was included in the multivariate Poisson regression model (Table 2, model 2), most of the associations between CNRs and TB control indicators became weaker.

There was a strong association between CNR and region ($p<0.001$) when zone was not in the model. The CNR was 1.3 times (95% CI 1.2-1.4) and 1.6 times (95% CI 1.5-1.7) higher in communes in the central and southern region, respectively, than in those in the northern region.

Some significant interactions were observed that showed relevant differences in stratum-specific rate ratios. Compared with those in the Red River Delta, communes with ethnic minorities in the North West Highlands had 2.1 times (95% CI 1.9-2.4) higher CNR. In the Central coast area, communes in districts that did not require user fees for smear examination had 2.0 (1.7-2.4) times higher CNR in comparison with districts that did.

**Table 1. Characteristics, Case notification rates uni- and multivariate analysis of determinants associated with case notification rate in 10,286 communes in Vietnam.**

| | Number of communes (%) | CNR | | Univariate | | Multivariate-model 1 | | Multivariate-model 2 | |
|---|---|---|---|---|---|---|---|---|---|
| | | per 100,000 | 95% CI | IRR | 95%CI | aIRR (1) | 95%CI | aIRR (2) | 95%CI |
| Whole country | | 78.0 | 76.8-79.2 | | | | | | |
| **Demographic indicators** | | | | | | | | | |
| Zone (n=10,286) | | | | | | | | | |
| Red River Delta | 2,172 (21.1) | 46.8 | 44.8-49.2 | 1.00 | | 1.00 | | 1.00 | |
| North-East Highlands | 2,050 (19.9) | 117.2 | 112.8-121.6 | 2.50 | 2.35-2.65 | 1.87 | 1.71-2.04 | 1.53 | 1.40-1.67 |
| North-West Highlands | 558 (5.4) | 74.4 | 67.6-81.6 | 1.58 | 1.43-1.75 | 1.40 | 1.24-1.58 | 1.30 | 1.15-1.46 |
| North Central Coast | 1,668 (16.2) | 60.8 | 57.6-64.0 | 1.29 | 1.21-1.38 | 1.16 | 1.06-1.26 | 1.12 | 1.02-1.21 |
| Central Coast | 779 (7.6) | 94.0 | 89.2-99.2 | 2.00 | 1.87-2.14 | 2.06 | 1.91-2.22 | 1.86 | 1.72-2.00 |
| Central Highlands | 434 (4.2) | 75.6 | 65.6-77.6 | 1.52 | 1.39-1.67 | 1.58 | 1.41-1.77 | 1.40 | 1.25-1.56 |
| South-East Highlands | 1,182 (11.5) | 79.6 | 76.8-82.4 | 1.70 | 1.60-1.80 | 2.00 | 1.86-2.14 | 1.87 | 1.75-2.01 |
| Mekong River Delta | 1,443 (14.0) | 93.6 | 90.8-96.4 | 1.99 | 1.89-2.10 | 1.99 | 1.86-2.12 | 1.75 | 1.63-1.87 |
| Urban/rural status (n=10,286) | | | | | | | | | |
| Urban | 1,400 (13.6) | 72.8 | 72.0-73.6 | 1.00 | | 1.00 | | 1,00 | |
| non-urban | 8,886 (86,4) | 94.8 | 94.0-95.2 | 1.17 | 1.12-1.21 | 1.25 | 1.19-1.32 | 1.33 | 1.26-1.41 |
| Ethnicity (n=10,286) | | | | | | | | | |
| Kinh | 6,053 (63.7) | 73.2 | 72.0-74.8 | 1.00 | | 1.00 | | 1.00 | |
| Ethnic minority | 319 (3.1) | 88.4 | 76.0-101.6 | 1.20 | 1.04-1.39 | 1.18 | 1.01-1.38 | 1.10 | 0.94-1.28 |
| Combination | 3,412 (33.2) | 87.6 | 85.2-90.0 | 1.19 | 1.16-1.24 | 1.01 | 0.97-1.06 | 1.00 | 0.95-1.04 |
| Poverty (n=10,228) | | | | | | | | | |
| Non-poor | 7,773 (76.0) | 77.6 | 76.0-78.8 | 1.00 | | 1.00 | | 1.00 | |
| Poor | 2,455 (24.0) | 82.0 | 78.8-85.6 | 1.06 | 1.01-1.11 | 1.02 | 0.97-1.08 | 1.03 | 0.98-1.09 |

**Table 1. Continued**

| | Number of communes (%) | CNR | | Univariate | | Multivariate-model 1 | | Multivariate-model 2 | |
|---|---|---|---|---|---|---|---|---|---|
| | | per 100,000 | 95% CI | IRR | 95%CI | aIRR (1) | 95%CI | aIRR (2) | 95%CI |
| Distance from communal health post to district TB unit (n=10,189) | | | | | | | | | |
| <5km | 2,422 (23.8) | 86.4 | 85.6-88.8 | 1.00 | | 1.00 | | 1.00 | |
| 5-15km | 4,365 (42.8) | 76.8 | 75.2-78.8 | 0.89 | 0.86-0.92 | 0.78 | 0.75-0.82 | 0.82 | 0.79-0.86 |
| >15km | 3,402 (33.4) | 70.8 | 68.8-73.2 | 0.82 | 0.79-0.85 | 0.65 | 0.62-0.68 | 0.70 | 0.67-0.74 |
| **Tuberculosis control indicators** | | | | | | | | | |
| Number of health care staff in commune (*) (n=9,818) | | | | | | 0.96 (#) | 0.95-0.98 | 1.00 (#) | 0.98-1.01 |
| <1,000 | 2,887 (29.4) | 99.2 | 95.2-103.6 | 1.00 | | | | | |
| 1,000-1,500 | 2,368 (24.1) | 75.6 | 72.4-78.4 | 0.76 | 0.72-0.80 | | | | |
| 1,500-2,000 | 1,880 (19.2) | 71.2 | 68.8-74.0 | 0.72 | 0.68-0.76 | | | | |
| 2,000-3,000 | 1,679 (17.1) | 78.0 | 75.2-80.4 | 0.78 | 0.74-0.83 | | | | |
| >3,000 | 1,004 (10.2) | 79.6 | 77.2-82.4 | 0.80 | 0.76-0.85 | | | | |
| Number of TB staff in commune (n=10,129) | | | | | | | | | |
| 1 or more | 10,017 (98.9) | 78.0 | 76.8-79.2 | 1.00 | | 1.00 | | 1.00 | |
| None | 112 (1.1) | 78.4 | 61.2-98.4 | 1.00 | 0.80-1.27 | 0.75 | 0.58-0.97 | 0.86 | 0.66-1.11 |
| Number of microscopy centers in district (n=10,042) | | | | | | | | | |
| 1 center | 8,558 (85.2) | 76.0 | 74.4-77.2 | 1.00 | | 1.00 | | 1.00 | |
| 2 centers | 1,169 (11.6) | 91.2 | 87.6-95.2 | 1.20 | 1.15-1.26 | 1.18 | 1.12-1.25 | 1.13 | 1.07-1.19 |
| >2 centers | 315 (3.1) | 103.2 | 96.4-110.8 | 1.36 | 1.27-1.46 | 1.22 | 1.13-1.32 | 1.07 | 0.99-1.16 |
| User fees for smear examination (n=9,914) | | | | | | | | | |
| No | 2,218 (22.4) | 82.6 | 81.1-84.1 | 1.00 | | 1.00 | | 1.00 | |
| Yes | 7,696 (77.6) | 70.9 | 68.5-73.3 | 0.86 | 0.83-0.89 | 0.86 | 0.82-0.90 | 0.91 | 0.87-0.95 |

**Table 1. Continued**

| | Number of communes (%) | CNR | | Univariate | | Multivariate-model 1 | | Multivariate-model 2 | |
|---|---|---|---|---|---|---|---|---|---|
| | | per 100,000 | 95% CI | IRR | 95%CI | aIRR (1) | 95%CI | aIRR (2) | 95%CI |
| X-ray service available in district (n=9,535) | | | | | | | | | |
| Yes | 569 (6.0) | 77.6 | 76.4-79.2 | 1.00 | | 1.00 | | 1.00 | |
| No | 8,966 (94.0) | 59.6 | 55.6-63.6 | 0.76 | 0.71-0.82 | 0.69 | 0.63-0.75 | 0.73 | 0.67-0.80 |
| Tuberculosis case-finding (CF) method applied in district | | | | | | | | | |
| Passive CF only | 6,348 (62.1) | 68.4 | 67.2-70.0 | 1.00 | | 1.00 | | 1.00 | |
| Passive and active CF | 3,873 (37.9) | 102.4 | 100.0-105.2 | 1.49 | 1.45-1.54 | 1.40 | 1.33-1.45 | 1.31 | 1.26-1.38 |
| Suspect rate | | | | | | | | 1.05 (‡) | 1.05-1.06 |

CNR: case notification rate
IRR: Incidence rate ratio in the univariate model
aIRR(1): adjusted incidence rate ratio in the Poisson regression model with all variables excepted region and TB suspect
aIRR(2): adjusted incidence rate ratio in the Poisson regression model with all variables excepted region
(*) number of inhabitants per health care staff
(#) variable fitted as continuous variable
(‡) measure for each increase in suspect rate per 1,000 population
All p-values based on likelihood ratio X2 test for excluding the variable from the model were <0.001, except for ethnicity and poverty (p>0.05)

**Table 2. Suspect rates (/1,000) and univariate-multivariate of risk factors associated with suspect rates in 6,348 communes applying passive case-finding methods only in Vietnam.**

| | | Suspect rate | | Univariate | | Multivariate | |
|---|---|---|---|---|---|---|---|
| | N (%) | /1,000 | 95% CI | IRR | 95%CI | aIRR | 95%CI |
| Whole country | 6.348 | 7.07 | 7.02-7.11 | | | | |
| **Demographic indicators** | | | | | | | |
| Zone | | | | | | | |
| Red River Delta | 2,018 (31.8) | 4.09 | 4.02-4.15 | 1.00 | | 1.00 | |
| North-East Highlands | 580 ( 9.1) | 18.19 | 17.85-18.53 | 4.45 | 4.34-4.56 | 5.67 | 5.48-5.86 |
| North-West Highlands | 213 ( 3.4) | 15.01 | 14.49-15.54 | 3.67 | 3.53-3.81 | 4.42 | 4.22-4.62 |
| North Central Coast | 542 ( 8.5) | 6.63 | 6.46-6.80 | 1.62 | 1.57-1.67 | 2.03 | 1.95-2.11 |
| Central Coast | 551 ( 8.7) | 8.70 | 8.53-8.87 | 2.13 | 2.08-2.18 | 2.60 | 2.53-2.67 |
| Central Highlands | 186 ( 2.9) | 5.62 | 5.40-5.84 | 1.37 | 1.32-1.43 | 1.60 | 1.52-1.68 |
| South-East | 992 (15.6) | 6.89 | 6.80-6.99 | 1.69 | 1.65-1.72 | 1.88 | 1.84-1.93 |
| Mekong River Delta | 1,266 (19.9) | 7.93 | 7.84-8.03 | 1.94 | 1.90-1.98 | 1.81 | 1.77-1.85 |
| Urban/rural status | | | | | | | |
| Urban | 1,022 (16.1) | 6.43 | 6.34-6.52 | 1.00 | | 1.00 | |
| non-urban | 5,326 (83.9) | 7.25 | 7.20-7.30 | 1.13 | 1.11-1.15 | 1.41 | 1.38-1.44 |
| Ethnicity | | | | | | | |
| Kinh | 4,431 (69.8) | 6.53 | 6.48-6.58 | 1.00 | | 1.00 | |
| EM | 222 ( 3.5) | 16.85 | 16.20-17.53 | 2.58 | 2.48-2.69 | 1.01 | 0.96-1.06 |
| Combination | 1,695 (26.7) | 8.05 | 7.96-8.15 | 1.23 | 1.22-1.25 | 1.05 | 1.03-1.07 |
| Poverty | | | | | | | |
| Non-poor | 5,125 (80.9) | 6.82 | 6.78-6.87 | 1.00 | | 1.00 | |
| Poor | 1,209 (19.1) | 8.74 | 8.60-8.88 | 1.28 | 1.26-1.30 | 1.06 | 1.03-1.08 |
| Distance from communal health post to district tuberculosis unit (n=10,189) | | | | | | | |
| <5km | 1,644 (26.0) | 7.95 | 7.87-8.04 | 1.00 | | 1.00 | |
| 5-15km | 2,826 (44.6) | 6.73 | 6.67-6.80 | 0.85 | 0.83-0.86 | 0.73 | 0.72-0.75 |
| >15km | 1,862 (29.4) | 6.52 | 6.44-6.61 | 0.82 | 0.81-0.83 | 0.59 | 0.58-0.60 |

**Table 2. Continued**

| | | Suspect rate | | | Univariate | | Multivariate |
|---|---|---|---|---|---|---|---|
| | N (%) | /1,000 | 95% CI | IRR | 95%CI | aIRR | 95%CI |
| **Tuberculosis control indicators** | | | | | | | |
| Number of health care staff in commune (*) | | | | | | 0.88 (#) | 0.87-0.89 |
| <1,000 | 1,190 (19.9) | 12.18 | 11.95-12.41 | 1.00 | | | |
| 1,000-1,500 | 1,433 (23.9) | 7.58 | 7.47-7.70 | 0.62 | 0.61-0.64 | | |
| 1,500-2,000 | 1,316 (22.0) | 6.86 | 6.76-6.96 | 0.56 | 0.55-0.58 | | |
| 2,000-3,000 | 1,323 (22.1) | 7.42 | 7.33-7.50 | 0.61 | 0.60-0.62 | | |
| >3,000 | 734 (12.2) | 5.96 | 5.88-6.05 | 0.50 | 0.48-0.50 | | |
| Number of TB staff in commune | | | | | | | |
| 1 or more | 6,321 (99.9) | 7.05 | 7.01-7.10 | 1.00 | | 1.00 | |
| None | 2 ( 0.003) | 18.08 | 14.50-22.28 | 2.56 | 2.08-3.16 | 3.01 | 2.44-3.71 |
| Number of microscopy centers in district | | | | | | | |
| 1 center | 5,172 (83.5) | 6.61 | 6.56-6.66 | 1.00 | | 1.00 | |
| 2 centers | 864 (14.0) | 8.51 | 8.38-8.65 | 1.29 | 1.26-1.31 | 1.14 | 1.12-1.16 |
| >2 centers | 153 ( 2.5) | 13.43 | 13.10-13.77 | 2.03 | 1.98-2.09 | 2.25 | 2.18-2.32 |
| User fees for smear examination | | | | | | | |
| No | 4,914 (81.1) | 7.25 | 7.20-7.30 | 1.00 | | 1.00 | |
| Yes | 1,148 (18.9) | 2.00 | 1.88-2.13 | 1.01 | 1.00-1.03 | 1.14 | 1.12-1.16 |
| X-ray service available in district | | | | | | | |
| Yes | 5,706 (93.8) | 7.07 | 7.02-7.12 | 1.00 | | 1.00 | |
| No | 376 ( 6.2) | 6.36 | 6.20-6.52 | 0.90 | 0.88-0.92 | 0.82 | 0.79-0.84 |

IRR: Incidence rate ratio in the univariate model
aIRR(1): adjusted incidence rate ratio in the Poisson regression model with all variables excepted region and TB suspect
(*) number of inhabitants per health care staff
(#) variable fitted as continuous variable

Among communes classified as poor, the CNR in the Central Coast area was 2.1 (1.5-3.0) times higher than in the Red River Delta (Figure 2).

Overall 2.2 per 1,000 population had been examined by direct microscopy on suspicion of TB in the study period. The estimated suspect rate for 2003 was 9.0/1,000 (95% CI 9.0-9.0). We limited the analysis of the suspect rate to 6,348 (62%) communes that applied passive case finding of tuberculosis suspects only (Table 2). A Poisson regression model of the suspect rate that also included communes that applied active case finding indeed showed significant and relevant interaction with case finding method for many of the variables (data not shown). The proportion of the population examined was slightly higher in the central (7.8/1,000; 95%CI 6.3-6.5) and southern region (7.5/1,000; 7.4-7.6) compared to the northern region (6.4/1,000; 6.3-6.5). There was substantial variation by zone, with the largest difference within the northern region (4.1/1,000 in the Red River delta and 18.2/1,000 in the North East Highlands, Figure 2).

In the multivariate model (Table 3), the suspect rate showed no relevant association with ethnic composition or poverty status of the commune. The suspect rate was strongly associated with zone. Other variables that showed associations of relevant size were urbanity (higher rates in non-urban compared to urban communes); distance from the commune to the DTU (decreasing rate with increasing distance); number of health care and TB staff in the commune (increasing rate with increasing number); and time since full implementation of the DOTS strategy (increasing rate with increasing period). The effect of user fees and availability of x-ray services was limited.

Analyses of interactions showed considerable variation in suspect rate between zones within strata of other variables. Taking the Red River Delta as the reference category, suspect rates were higher in the North-East Highlands and the Mekong River Delta among communes classified as poor (adjusted rate ratio (aRR) 3.0, 95% CI 2.9-3.1, and 2.5, 95% CI 2.4-2.6, respectively) as well as among communes with ethnic minorities (aRR 2.7, 95% CI 2.6-2.8, and 2.2, 95% CI 2.2-2.3, respectively). Suspect rates were also higher in the North-East Highlands among communes located at less than 5 km distance from the DTU (aRR 4.9, 95% CI 4.7-5.1), and in the Central Coast and Mekong River Delta zones among communes located at more than 15 km distance from the DTU (aRR 2.2 , 95% CI 2.0-2.3, and aRR 2.5, 95% CI 2.3-2.6, respectively, Figure 2).

Because suspects include patients who were diagnosed as smear-positive, we repeated the analyses using the rate of suspects who remained smear-negative instead of the suspect rate. These showed similar results; all incidence rate ratio's for associations with the case notification rate were within 5% of those estimated from the models based on the suspect rate (data not shown).

## DISCUSSION

We found substantial variation in TB case notification rates across the country. Geographic area, urbanity and distance to the district TB unit were determinants of this variation, also

after controlling for suspect rate, whereas poverty and ethnic composition of the commune were not. This suggests that geographic and urban-rural variations in TB case notification rates in Vietnam reflect, at least in part, differences in TB incidence. Availability of health care and TB staff in the commune and of microscopy centres and X-ray facilities in the district, as well as user fees and case finding methods, all affected case notification rates. Much of these associations disappeared when adjusting for suspect rate, suggesting that the suspect rate is "on the causal pathway" between these indicators and the case notification rate, and that the suspect rate is indeed a useful summary indicator of access to diagnosis and case finding efforts. The suspect rate, limited to districts applying passive case finding only, strongly depended on availability of commune health care and TB staff, on presence of microscopy centres in the district and on distance to the district TB unit, but hardly on user fees and availability of X-ray facilities. Moreover, it was itself associated with geographic area and urbanity. The suspect rate was also not associated with poverty or ethnicity.

The remarkable geographic variations partially reflect a north-south gradient in TB incidence. Because of strong overlap between geographic zones and regions we were unable to test both in a single multivariate model, but the model adjusting for suspect rate showed a clear gradient. The causes of this gradient are unknown. It may reflect differences in TB control between the north and the south before unification in 1975, in prevalence of infections with non-tuberculosis mycobacteria or in genotype distribution [13,14]. Apart from this gradient, there are substantial differences between administrative zones that probably reflect at least in part differences in altitude. Lower TB incidence at high altitude has been observed in other countries [15,16]. It is yet unclear to what extent this reflects differences in population density.

The suspect rate also showed considerable variation by zone. This appears to reflect relatively low rates in the Red River Delta and relatively high rates in the North-East and North-West Highlands. In these highlands, the high TB suspect rate may reflect high incidence or prevalence of other respiratory diseases due to the cold climate and the tobacco smoking and cooking habits (with much indoor air pollution) of the predominant ethnic minority population

We found that both the CNR and suspect rate were lower in urban areas. The likely explanation is that more patients go to the private sector [17] or to provincial health care facilities, but also that more selection takes place before smear examinations are done, e.g by x-ray. It thus cannot be concluded from these data that TB incidence is lower in urban than in non-urban areas.

Studies from low TB-prevalence countries have shown strong associations of TB incidence with poverty and ethnicity [18-20]. In addition, poverty may limit access to health services [21,22]. In 2004, 20% of the Vietnamese population lived below the poverty line, and ethnic minorities accounted for 13% of the country's population [23]. Ethnic minorities in Vietnam are also relatively poor. Whereas the majority Kinh population inhabit mainly the fertile lowlands in the river deltas and along the coast, these minorities live scattered across

the mountain areas that cover two-thirds of the country's territory, extending from the north to the south [24]. An unexpected finding in our study was that, at the commune level, neither poverty nor ethnicity were associated with notification or suspect rate. This could be explained by recent improvements in access of the poor and ethnic minorities to basic health services, but it may also be that poverty and ethnicity at commune level insufficiently reflect the effects of individual (household) poverty and ethnicity in this analysis. Forthcoming results of a tuberculosis prevalence survey in which data on poverty and ethnicity are collected at the household level will shed more light on this.

The suspect rate per commune clearly decreased with increasing distance to the district TB unit. Apparently, distance is a key factor determining access to TB services. The diagnosis of TB can in Vietnam only be made at district centres and requires the submission of 3 sputum samples. This makes it difficult for the patients who live far away and do not have their own means of transport. The CNR remained somewhat lower in communes at large distances despite adjustment for suspect rate, suggesting there is also some difference in TB incidence in the peripheries of districts where people live more scattered and their contact rate may be lower compared with those who live in more density populated district centres.

Our data and analyses have a number of limitations. When controlling for variation in TB suspect rate, the association between indicators of TB control response and CNR became weaker, but some of these control indicators remained independently associated. This may mean that the suspect rate does not capture all variation in health care response, e.g. because the proportion of examined patients who were truly clinically suspect of having TB may vary between communes and districts. Alternatively, the association between some of the TB control indicators and the CNR may in fact be reverse. For example, active case finding may be practiced *because* a district has a high TB incidence. Another limitation of the use of the suspect rate in our analysis may be that this is composed of 3 elements: background rate of cough (i.e. due to other causes than TB) and diagnostic effort of NTP facilities, but also TB incidence. By including suspect rate in the model, we may thus have over-adjusted to some extent the variation in CNRs because we partially controlled for variations in incidence. However, we obtained nearly identical results when we replaced in our analyses the suspect rate by the rate of suspects who remained smear-negative, suggesting that this effect is very limited.

Finally, data were limited to the district TB units. Patients who went to provincial TB hospitals or private health care providers for diagnosis and treatment of TB were not included in our analyses. This may have resulted in underestimation of suspect rates, in particular in urban areas [17].

## CONCLUSIONS

This study suggests that geographical variations in TB notification in Vietnam largely reflect true epidemiological differences in TB distribution. Notification rates vary remarkably by latitude, zone and urbanity and are not associated with poverty or ethnicity at commune level. Distance to the district health centre, availability of health care and TB

staff and the number of microscopy centres in the district are key factors determining access to TB services. The TB suspect rate appears to be a useful summary indicator of the diagnostic effort in this setting.

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# Chapter 6

# Tuberculosis epidemiology in six provinces of Vietnam after the introduction of the DOTS Strategy

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**ABSTRACT**

*Setting:* Six provinces in Vietnam where the DOTS Strategy was introduced in 1989.

*Objective:* To assess the impact of improved tuberculosis (TB) control on TB epidemiology in Vietnam.

*Methods:* Data from the surveillance system in the period 1990–2003 were analysed to assess trends of notification rates and the mean ages of notified cases. Data from repeated tuberculin surveys in the period 1986– 2002 were estimated to assess the prevalence of TB infection, the annual risk of infection and its trend using various cut-off points in those with and without bacilli Calmette-Guérin (BCG) scar.

*Results:* Age-standardised notification rates in the period 1996–2003 declined significantly, by 2.6% to 5.9% per year, in five provinces. However, in four provinces notification rates in the age group 15–24 years increased significantly, by 4.5% to 13.6% per year, during this period. The mean age of newly diagnosed patients with smear-positive TB increased up to 1995 but decreased thereafter. The annual risk of TB infection showed a significant annual decrease (4.9% per year) in one province in surveys performed between 1986 and 1997, and in two provinces (6.6% and 14.7%) in surveys conducted between 1993 and 2002.

*Conclusion:* These data suggest limited impact to date of the DOTS Strategy in Vietnam.

## INTRODUCTION

Tuberculosis (TB) remains a global health problem [1]. Mathematical models predict that if at least 70% of incident cases of smear-positive TB are detected and treated, and at least 85% are cured, TB transmission will decline by 7% to 11% per year [2,3]. The World Health Organization (WHO) has therefore set these thresholds for case detection and cure rates as targets for its global DOTS Strategy [3,4]. The predicted reduction in transmission should result in a decrease in incidence of TB, an increase in the mean age of tuberculosis cases and a decline in the annual risk of tuberculosis infection (ARTI) [5].

Vietnam is among the 22 countries with the highest number of TB cases in the world [6]. The National Tuberculosis Programme (NTP) of Vietnam is the only TB control programme in a high-burden country that has met the WHO targets of a 70% case detection rate and an 85% treatment success rate [6,7].

To assess the impact of Vietnam's control strategy, we analyzed TB trends between 1986 and 2003 in six provinces using two indicators: the ARTI measured among schoolchildren, and TB case notifications and their age distribution. In these provinces, TB control was introduced in 1989 following the principles of what was later adopted by the WHO as the global DOTS Strategy [8]. Cure rates exceeded 85% from the early 1990s onwards. The gradual introduction of DOTS services in these provinces reached its current coverage in 1996. In the same year, the NTP introduced an incentive system to improve case detection. The estimated case detection rate has been above 70% since 1997 [7,8].

## METHODS

We obtained from the NTP numbers of notified cases of new smear-positive TB by 10-year age group in six provinces where tuberculin surveys have been conducted periodically (Figure 1). These were available from 1990 onwards. Population denominators were available from two censuses (1989 and 1999) and were inter- and extrapolated for the years 1990–2003 assuming exponential growth [9,10] To assess overall trends of case notification rates (CNRs), age-specific notification rates of each of the six provinces were standardised to the combined population of these provinces in 1999. In addition, we assessed the trends of CNRs separately for the age groups 15–24, 25–64 and ≥65 years by Poisson regression.

The study period was split into two periods, with 1995–1996 as the breakpoint, for two reasons. First, the estimated case-detection rate of the NTP was above 70% only after 1996 [7] and second, the expansion of DOTS facilities in the provinces included in this study did not reach its current level of population coverage until that year, and the introduction of an incentive system for detecting and treating TB cases in 1996 clearly increased case detection [8].

**Figure 1. Map of Vietnam with six study provinces indicated.**

As the mean age of the total population increased over the study period, we based the trend in mean age of TB cases on the age-standardised CNRs. From 1986 onwards, tuberculin surveys were carried out in these six selected provinces at 5-year intervals following the same study protocol. In each province, schools were selected randomly from all districts to obtain a number of non-bacille Calmette-Guérin (BCG) vaccinated children proportional to the district population size. All children enrolled in grade 1 and 2 of the selected schools were listed, along with their age and sex. During the survey, presence of a BCG scar was checked and recorded. Tuberculin testing was by the Mantoux method using 2 TU (in Hanoi and Ho Chi Minh City [HCMC] 1 TU) of PPD RT-23 with Tween 80 (Statens Seruminstitut, Copenhagen, Denmark) according to international guidelines [11,12]. The survey protocol was approved by the Research Board of the National Institute (now Hospital) of Tuberculosis and Respiratory Diseases, Hanoi.

The BCG vaccination policy in Vietnam is to immunize all children at birth. The prevalence of TB infection was estimated from tuberculin skin test (TST) results in children without a BCG scar. However, as a large proportion of children had a BCG scar and this proportion increased with time, comparisons between surveys were made for children without and those with a BCG scar.

The prevalence of infection was estimated as the proportion of children with a reaction of ≥10mm. In some provinces, many children had intermediate-size reactions that probably reflected cross-reactions to environmental mycobacteria [13,14]. As in those circumstances infection prevalence can only be estimated with uncertainty, we checked the robustness of the results by applying the 'mirror method' [15,16]. In this method, all those with a reaction size equal to the median reaction among TB patients are counted once, and those with larger reactions are counted twice to obtain the estimated number of infections. The rationale for this approach is that tuberculin reactions among confirmed TB patients are approximately normally distributed with a median of around 16mm, and tuberculin reactions of ≥16mm are rarely due to environmental mycobacteria infections [16]. An estimate of the median was obtained from tuberculin testing patients with smear-positive TB in the north, middle and south of Vietnam. Among these patients, the median ranged from 15 to 19mm. Accordingly, we used 15, 17 and 19mm as a median for the mirror method.

The ARTI has been defined as the fraction of the population that is infected or re-infected during a calendar year [17]. It was calculated as [18]:

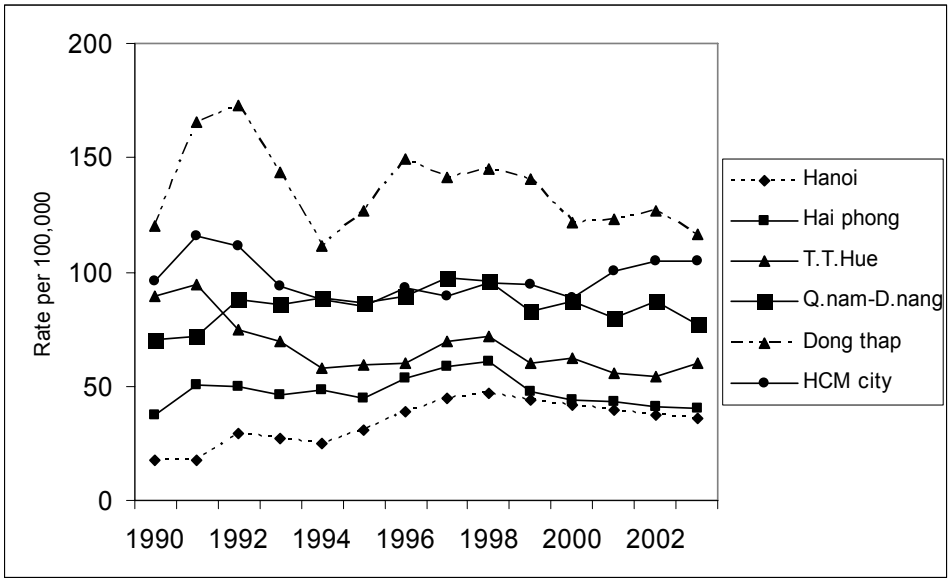
$$\text{ARTI} = 1 - (1 - \text{prevalence})^{1/\text{mean age}}$$

For age we used age at last birthday plus 0.5 years. Analyses were restricted to children aged 6–14 years. Provincial estimates were obtained as the prevalence
and ages averaged over all children included. Standard errors were corrected for the cluster design by calculating the variance of the prevalence over all schools.

**RESULTS**

Over the period 1990–1995, the overall age-standardised CNR of new smear-positive TB declined significantly by 3.3% to 9.2% per year in Thuathien-Hue, HCMC and Dongthap, while it increased significantly by 11.5% and 5.0% per year in Hanoi and Quangnam-Danang, respectively. It did not change in Haiphong (Figure 2, Table 1). Over the period 1996–2003, the overall age-standardised CNR declined significantly by 2.5% to 5.9% per year in all provinces except HCMC, showing a significant increase of 2.1% (Figure 2, Table 1).

**Figure 2. Age-standardised notification rates in six provinces of Vietnam, 1990-2003**




TT.Hue=Thua thien Hue; Q.nam-D.nang=Quang nam-Da nang; HCM city=Ho Chi Minh city

The age pattern of the trend in notification rates of new smear-positive TB differed between the two periods (Table 1). In the oldest age group, ≥65 years, CNRs predominantly increased over the period 1990–1995 (5/6 provinces, significant in 3/6), but predominantly decreased over the period 1996–2003 (5/6 provinces, significant in 3/6). In the youngest age group, 15–24 years (Figure 3), CNRs showed a more varied trend over the period 1990–1995, but a predominant increase over the period 1996–2003. Over the period 1996–2003, the youngest age group showed significant increases of 4.5% to 13.6% in four provinces, and less than average decreases in the remaining two. This trend partially counterbalanced significant decreases in CNRs of 3.0% to 6.7% per year that were observed over this period in the age group 25–64 years in all provinces except HCMC.

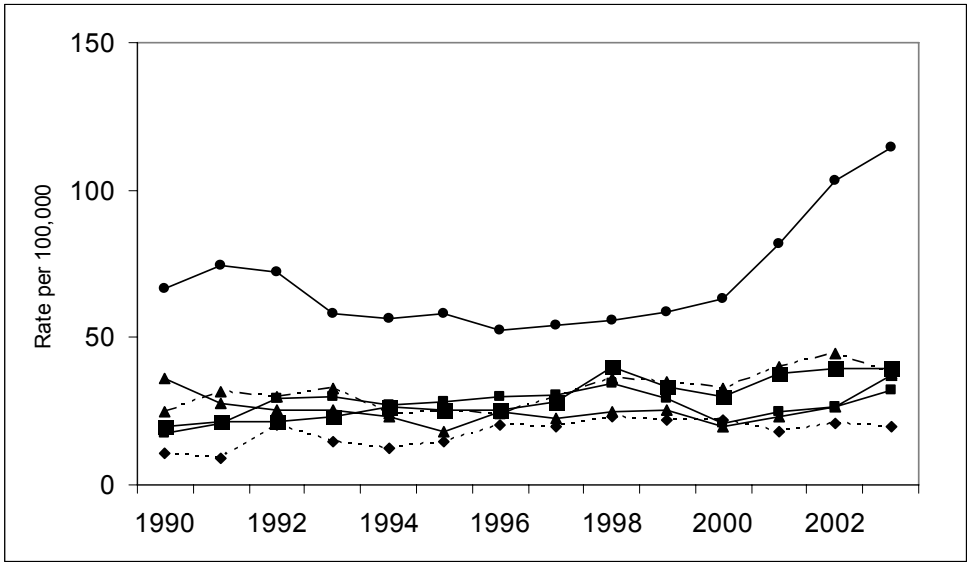
**Table 1. Age-adjusted trends in notification rate of new smear-positive tuberculosis in 6 provinces in Vietnam, 1990-2003, by time period and age group.**

| Province | Age, years | 1990-1995 % annual change (95% CI) | | 1996-2003 % annual change (95% CI) | |
|---|---|---|---|---|---|
| Hanoi | **All** | **11.5** | **(9.4-13.6) *** | **-2.6** | **(-3.4, -1.7) *** |
| | 15-24 | 6.3 | (0.5-12.6) * | -0.8 | (-3.5, 2.0) |
| | 25-64 | 10.6 | (8.2-12.9) * | -3.5 | (-4.5, -2.5) * |
| | 65+ | 22.9 | (16.4-29.8) * | 0.1 | (-1.9, 2.2) |
| Haiphong | **All** | **1.5** | **(-0.3-3.4)** | **-5.9** | **(-6.9, -4.9) *** |
| | 15-24 | 8.2 | (2.3-14.5) * | -1.7 | (-3.5, 1.6) |
| | 25-64 | 0.2 | (-1.9-2.3) | -6.7 | (-7.8, -5.5) * |
| | 65+ | 4.0 | (-1.1-9.4) | -5.1 | (-7.4, -2.8) * |
| Thuathien- | **All** | **-9.2** | **(-10.9- -7.4) *** | **-2.5** | **(-3.7, -1.3) *** |
| Hue | 15-24 | -10.9 | (-16.7- -4.7) * | 4.5 | (0.1, 9.1) * |
| | 25-64 | -10.9 | (-12.9- -8.9) * | -3.4 | (-4.8, -1.9) * |
| | 65+ | 0.7 | (-4.1-5.7) | -2.3 | (-4.9, 0.3) |
| Quangnam- | **All** | **5.0** | **(3.6-6.3) *** | **-2.8** | **(-3.5, -2.1) *** |
| Danang | 15-24 | 5.6 | (0.5-11.1) * | 5.3 | (2.6, 8.1) * |
| | 25-64 | 3.4 | (1.9-5.0) * | -3 | (-3.8, -2.1) * |
| | 65+ | 11.0 | (7.8-14.3) * | -4.9 | (-6.3, -3.4) * |
| HCMC | **All** | **-4.8** | **(-5.5- -4.1) *** | **2.1** | **(1.6, 2.5) *** |
| | 15-24 | -4.8 | (-6.6- -3.0) * | 13.6 | (12.3, 14.8) * |
| | 25-64 | -4.7 | (-5.5- -3.8) * | 0.4 | (-0.1, 0.9) |
| | 65+ | -5.6 | (-7.9- -3.2) * | -1.6 | (-2.9, -0.2) * |
| Dongthap | **All** | **-3.3** | **(-4.4- -2.1) *** | **-3.3** | **(-3.9, -2.6) *** |
| | 15-24 | -2.2 | (-7.1-3.0) | 6.1 | (3.1, 9.1) * |
| | 25-64 | -5.7 | (-6.9- -4.4) * | -3.8 | (-4.7, -3.0) * |
| | 65+ | 6.9 | (4.0-9.9) * | -3.9 | (-5.3, -2.5) * |

Age adjustment by Poisson regression, based on 10-year age categories. Minus sign (-) denotes decrease.
*: significant ($p<0.05$).
TB = tuberculosis; CI = confidence interval; HCM = Ho Chi Minh City

Over the period 1990–1995, the mean age of newly diagnosed patients with smear-positive TB increased significantly in Hanoi (average annual increase 0.58 years; 95% confidence interval [CI] 0.02–0.96), Quangnam-Danang (0.42; 95% CI 0.22–0.61) and Dongthap (0.64; 95% CI 0.39–0.89). In the period 1996–2003, the mean age declined significantly in Quangnam-Danang (average annual decrease 0.35 years; 95% CI 0.59–0.10), Dongthap (0.21; 95% CI 0.34–0.09) and HCMC (0.38; 95% CI 0.59–0.17).

**Figure 3. Notification rates in age group 15-24 years in six provinces of Vietnam, 1990-2003. Legend as for figure 2.**




In the tuberculin surveys, a total of 124 915 schoolchildren were listed in six provinces. Of 120 222 (96.2%) children who were eligible, tested and read for analysis, 29 527 (24%) were included in the study in the first period (1986–1991), 40 684 (34%) in the second (1993–1997) and 50 011 (42%) in the third (1998–2002) (Table 2). Of all children included, 52 742 (44%) had no BCG scar. The proportion of children without BCG scar decreased with time from 64% in the first to 57% in the second and 22% in the third survey period (Table 2).

The frequency distributions of non-zero tuberculin reactions among children without and those with BCG scar in the three periods showed no clear mode for the distribution among infected children, nor an antimode that separates reactions among infected and non-infected children (data not shown). A higher proportion of reactions in the range 4–20mm were observed among children with BCG scar compared to those without BCG scar in all three periods. However, the shape of the frequency distribution was similar for both in each of the three survey periods.

**Table 2. Schools selected and numbers of eligible children tested and read in tuberculin surveys in six provinces in Vietnam.**

| Province | 1986-1991 | | | 1992-1996 | | | 1997-2002 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Schools n | Children eligible, tested and read/children listed | Children without BCG scar n (%)* | Schools n | Children eligible, tested and read/children listed | Children without BCG scar n (%)* | Schools n | Children eligible, tested and read/children listed | Children without BCG scar n (%)* |
| Hanoi rural | | | | 34 | 11,453/11,459 | 8,480 (74) | 34 | 9,370/ 9,500 | 1,869 (20) |
| Hai phong | 21 | 7,518/ 7,692 | 6,081 (81) | 21 | 8,224/ 8,477 | 3,080 (37) | 21 | 7,039/ 7,137 | 1,283 (18) |
| Thua Thien Hue | 24 | 7,230/ 7,754 | 6,165 (85) | 35 | 7,235/ 7,543 | 3,446 (48) | 40 | 9,427/ 9,661 | 4,114 (44) |
| Quangnam-Da nang | | | | 30 | 9,808/ 9,816 | 5,745 (59) | 30 | 10,537/10,796 | 2,115 (20) |
| HoChi Minh City urban | 14 | 9,687/11,139 | 2,138 (22) | | | | 31 | 10,358/10,383 | 983 (10) |
| Dong thap | 14 | 5,092/ 5,628 | 4,544 (89) | 17 | 9,344/ 4,471 | 2,224 (56) | 20 | 3,280/ 3,459 | 538 (16) |
| Total | 73 | 29,527/32,213 | 18,865 (64) | 137 | 40,684/41,766 | 22,975 (57) | 176 | 50,011/50,936 | 10,902 (22) |

* Percentage of children eligible, tested and read
BCG = bacilli Calmette-Guénin

**Table 3. ARTI and percent change per year among children without BCG scar, based on TST in six provinces in Vietnam by various criteria for infection.**

| | Cut-off 10 mm | | Mirror method 15 mm | | Mirror method 17 mm | | Mirror method 19 mm | |
|---|---|---|---|---|---|---|---|---|
| | ARTI (%) | Annual change (%) | ARTI (%) | Annual change (%) | ARTI (%) | Annual change (%) | ARTI (%) | Annual change (%) |
| Hanoi rural[†] | | | | | | | | |
| 1993 | 0.83 | | 0.53 | | 0.33 | | 0.18 | |
| 1999 | 0.8 | -0.7 | 0.52 | -0.3 | 0.31 | -1.2 | 0.2 | 1.4 |
| Hai phong | | | | | | | | |
| 1990 | 1.21 | | 1.37 | | 1.1 | | 0.8 | |
| 1996 | 1.58 | 4.9 * | 1.54 | 2 | 1.12 | 0.3 | 0.81 | 0.2 |
| 2001 | 1.33 | -3.1 * | 1.4 | -1.8 | 0.89 | -4.1 | 0.52 | -7.1 |
| Thua thien Hue | | | | | | | | |
| 1991 | 2.97 | | 2.25 | | 1.33 | | 0.77 | |
| 1997 | 2.21 | -4.3 * | 1.43 | -6.0 * | 0.94 | -4.9 * | 0.6 | -3.7 * |
| 2002 | 0.95 | -11.4 * | 0.52 | -12.7 * | 0.25 | -14.7* | 0.11 | -16.3 * |
| Quang nam - Da nang | | | | | | | | |
| 1994 | 2.39 | | 1.71 | | 0.94 | | 0.6 | |
| 2000 | 1.57 | -5.7 * | 1.07 | -6.2 * | 0.57 | -6.6 * | 0.34 | -7.3 * |

**Table 3. Continued**

| | Cut-off 10 mm | | Mirror method 15 mm | | Mirror method 17 mm | | Mirror method 19 mm | |
|---|---|---|---|---|---|---|---|---|
| | ARTI (%) | Annual change (%) | ARTI (%) | Annual change (%) | ARTI (%) | Annual change (%) | ARTI (%) | Annual change (%) |
| HoChiMinh City (urban) | | | | | | | | |
| 1986 | 2.63 | | 2.13 | | 0.91 | | 0.39 | |
| 1998 | 2.52 | -0.4 | 2.38 | 1 | 1.24 | 3.1 | 0.51 | 2.8 |
| Dong thap | | | | | | | | |
| 1990 | 1.56 | | 1.14 | | 0.63 | | 0.31 | |
| 1995 | 2.03 | 6 | 1.19 | 0.9 | 0.73 | 3 | 0.41 | 6.8 |
| 2001 | 2.05 | 0.1 | 1.4 | 2.9 | 0.61 | -2.6 | 0.31 | -4 |

Annual change: average annual change expressed as percentage of the ARTI observed in the previous survey. Minus sign (-) denotes decrease.
† 1 TU PPD-RT23 instead of 2 TU.
* Significant ($p<0.05$).
ARTI : annual risk of tuberculosis infection; BCG = bacilli Calmette-Guénin; TST = tuberculin skin test.

The prevalence of TB infection varied substantially by definition of a positive test, by province and by period, both among children without (Table 3) and among those with BCG scars (data not shown). Among the provinces where a survey conducted in the period 1993–1997 could be compared with a previous survey, the ARTI showed predominantly non-significant increases in Haiphong and Dongthap, and a 3.7–6.0% annual decrease in Thuathien-Hue that was significant by two of the four definitions used. Among provinces where a survey done in the period 1999–2002 could be compared to a survey done in the mid-1990s, the ARTI showed no significant changes in Hanoi and Dongthap, a predominantly non-significant decrease in Haiphong and decreases of 5.7–7.3% and 11.4–16.3% per year in Thuathien-Hue and Quangnam-Danang, respectively. For both, these trends were significant across all definitions. In HCMC, where surveys were performed in 1986 and 1998, no significant change in ARTI was observed. A similar pattern was observed among children with BCG scar (data not shown).

## DISCUSSION

We observed significant decreases in CNR of new smear-positive TB over the period 1996–2003 of 2.5% to 5.9% per year in all provinces except HCMC. Over the same period, the ARTI decreased significantly in two of six provinces by 6.6% to 14.7% per year. This suggests that control efforts are beginning to have an impact on the TB epidemic in Vietnam. Over this period we also, however, found significant increases in CNR in the youngest age group (15–24 years) in four provinces, and a less than average decrease in the remaining two, which is reflected in a lack of increase in mean age of notified cases in all provinces. This partly offset stronger decreases in CNR in the other age groups. Thus, a new epidemic wave may be underway, in particular in HCMC, where the CNR in the youngest age group increased by 13.6% per year.

The decrease in CNR and ARTI was observed mainly from 1996 onwards. When improving case detection, notification rates will increase initially, and thus a decline in incidence can be detected through notification only after the case detection rate has stabilised at this higher level. Second, tuberculin surveys measure impact on transmission with considerable delay, as the risk of infection represents the average risk over the lifetime of the children included, i.e., >6.5 to 8.5 years before the survey. A decline in ARTI would thus not be expected before 1996. The estimates for the period 1996–2003 thus better reflect the impact of TB control than those for the entire period.

The increasing CNRs in the oldest age group in four provinces in this period probably reflected improving case finding, i.e., the expanding programme coverage particularly benefited the old. The increase in mean age of TB patients observed in the period 1990–1995 thus does not reflect declining transmission, as was observed in Europe when countries changed from a high-prevalence to a low-prevalence situation [5].

The increase in CNR among the youngest age group over the most recent period (1996–2003) is cause for concern. Apart from Thuathien-Hue, where the ARTI declined between 1991 and 1997, we could not show a clear increase or decrease in ARTI in the period when

this age group was eligible for TST. Therefore, the increase in transmission that resulted in increasing notification rates since 1996 probably occurred very recently, and the ARTI may have increased again since the most recent surveys in our study. Nevertheless, even in the older age groups, where CNRs had decreased since 1996, the extent of decline is less than the 7–11% annual decrease in TB incidence that is predicted to occur when the WHO targets of 70% case detection rate and 85% cure rate are met [2,3].

One explanation for this limited impact of TB control is the emerging human immunodeficiency virus (HIV) epidemic [19]. The number of HIV-infected TB cases has increased considerably since 2000 in Haiphong and HCMC [19,20]. The prevalence of HIV infection among patients diagnosed with TB as estimated by sentinel surveillance was 11.8% in Haiphong and 9.3% in HCMC in 2002 (NTP, unpublished). This HIV epidemic is currently concentrated in drug users and commercial sex workers [19]. Studies are underway to assess the impact of HIV on TB CNRs, particularly in the younger age groups.

Possible other explanations for the limited impact of TB control include the rapid urbanisation and population movement since the economic liberalization of the late 1980s [9,10] and the spread of new *Mycobacterium tuberculosis* strains such as the Beijing genotype [21]. Furthermore, case detection and cure rates may have been overestimated. This may be the case in particular in urban areas where the private health sector is growing rapidly, often with poor outcomes of TB treatment [22,23]. However, cure rates may be lower than reported in the NTP, and operational studies are being conducted to evaluate these. The case detection rates reported by the WHO are based on rather uncertain estimates of TB incidence. If TB incidence were underestimated, the case detection rate would be overestimated. A TB prevalence survey would help establish the true burden of TB in the country, as well as provide a baseline against which the impact of the programme on the TB epidemic can be evaluated.

This study has limitations. First, there are methodological difficulties in the interpretation of tuberculin survey data [16,24]. These include rounding to multiples of five, problems of interpretation following BCG vaccination, representation of non-vaccinated children, misclassification of vaccination status (not all vaccinated children develop a typical scar), influence of infection with environmental mycobacteria, and the uncertain role of tuberculin reversion [16,24]. However, estimates of trend should be fairly robust and not strongly depend on these factors [24]. With few exceptions, our trend estimates did not depend on the cut-off point used and were similar for those with and without BCG scar.

Second, there is a strong urban bias in the provinces included in this analysis. Due to migration from rural areas, districts that were predominantly rural during the first survey may have become predominantly urban by the time of the third, in particular in Hanoi and HCMC [9,10]. TB incidence tends to be higher in urban than in rural settings, and such demographic shifts may have caused a paradoxical increase in incidence.

## CONCLUSIONS

Our data suggest limited impact to date of the DOTS Strategy in Vietnam despite high case detection and cure rates. However, we did observe the beginning of a decline in transmission and incidence after DOTS coverage and case detection had reached its current levels.

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# Chapter 7

# Survival and relapse rate of tuberculosis patients who successfully completed treatment in Vietnam

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**ABSTRACT**

*Setting*: Reported tuberculosis (TB) cure rates are high in Vietnam with the 8-month short-course chemotherapy regimen. However, long-term treatment outcomes are unknown.

*Objective:* To assess survival and relapse rates among patients successfully treated for new smear-positive pulmonary tuberculosis (PTB).

*Methods:* A cohort of patients treated in 32 randomly selected districts in northern Vietnam were followed up 12–24 months after reported cure or treatment success for survival and bacteriologically confirmed relapse. Measurements included sputum smear examination, culture and interview for recent treatment history.

*Results:* Of 304 patients included in the study, no information was available for 31 (10%) and 19 (6%) had died. Bacteriology results were available for 244 (80%). The median interval between treatment completion and follow-up was 19 months. Relapse was recorded in 21/244 (8.6%, 95% CI 5.4–13), including 9 (4%) with positive sputum smears, 3 (1%) with negative smears but positive culture and 9 (4%) who had started TB retreatment. Four of 12 culture-positive relapse cases (33%) had multidrug-resistant strains. If the definition of relapse was extended to include death, reportedly due to TB, the relapse proportion was 26/263 (9.9%, 95% CI 6.6–14).

*Conclusion:* A substantial proportion of patients (15%) had died or relapsed after being successfully treated for TB in northern Vietnam.

## INTRODUCTION

The World Health Oragnization (WHO) global strategy for tuberculosis (TB), the DOTS Strategy, recommends the use of short-course chemotherapy (SCC) for pulmonary tuberculosis (PTB). With SCC, 82% of all new smear-positive cases notified in DOTS programmes worldwide completed treatment successfully, and 1.7% failed [1]. However, patients who are cured with SCC may develop TB disease again with the strain that caused the original disease episode [2]. In the DOTS Strategy a relapse case is defined as a patient previously declared cured, but with a new episode of bacteriologically positive TB [1]. Globally, 265 918 relapse cases were notified in 2004 [1]. Case fatality is higher among relapse cases than among new cases [1]. Therefore, relapse TB is a relevant cause of morbidity and mortality. In addition, relapse cases likely contribute to TB transmission.

In an international multi-centre randomised controlled trial, the combined failure and relapse rate was 10% for the 8-month SCC regimen with ethambutol (EMB, E) and isoniazid (INH, H) in the continuation phase and 5% for the 6-month SCC regimen with rifampicin (RMP, R) throughout [3]. In many countries, the 8-month regimen is used because of financial constraints and because it is considered to carry a lower risk of inducing multidrug resistance (MDR) [4].

The relapse rate under routine practice may differ from that in a clinical trial because of differences in TB and human immunodeficiency virus (HIV) epidemiology, different patient populations and possibly less strict supervision of drug intake. More importantly, in many low-income countries, cure is defined routinely by a single negative sputum smear at treatment completion plus a negative smear on at least one previous occasion [5]. In clinical trials, however, cure is based on culture, which is more sensitive than smear microscopy [6]. In routine practice where cure is based on smear microscopy, treatment failures can thus be missed. Such cases will be in addition to true relapses, in which the patient is smear- and culture-negative at the end of treatment but develops TB again with the same infecting strain [2].

Few data are available on relapse rates in DOTS programmes. Numbers of diagnosed relapse cases are routinely collected [1], but time intervals from treatment completion to relapse, and therefore relapse rates, are generally unknown. Furthermore, these cases have been diagnosed because patients report with symptoms. Relapse patients who die, eventually self-heal or are treated outside the National Tuberculosis Programme (NTP) will thus not be included. The relapse rate with culture-based active follow-up under programme conditions is known in only a few settings, such as in India [7].

This study aims to assess survival and the bacteriologically confirmed relapse rate 12–24 months after treatment completion among new smear-positive PTB patients diagnosed and treated by the Vietnam NTP with reported cure or treatment completion.

Vietnam is a high-burden country for TB; 58 389 new smear-positive patients were notified in 2004 (70 per 100 000 population) [1]. The DOTS Strategy has been implemented

nationwide since 2000 [8]. The standard NTP treatment regimen for new patients consists of daily streptomycin (SM, S), INH, RMP and pyrazinamide (PZA, Z) for 2 months, followed by daily INH and EMB for 6 months (2SHRZ/6HE). The prevalence of MDR among new smear-positive TB patients was 2.3% in a nationwide survey conducted in 1996–1997 [9]. The estimated prevalence of HIV infection in the adult population was 0.5% in 2005 (range, 0.3–0.9%) [10]. Since 1997, the NTP has reported high treatment success rates of over 90% among new smear-positive TB cases and a 1% failure rate in 2003 [1]

## STUDY POPULATION AND METHODS

The study was restricted to northern Vietnam for logistical reasons. We randomly selected 32 of 298 NTP TB districts.

Eligible for inclusion in the cohort in the selected districts were patients diagnosed with previously untreated smear-positive TB who had started treatment between 1 April 2002 and 1 April 2003 and had cure or treatment completion as the reported treatment outcome. Excluded were patients aged ≤15 years and patients living outside the district at the time of treatment.

The sample size was based on an estimated relapse rate of 10% and around a desired confidence interval (CI) of 5–15% and calculated at 304 patients, allowing 10% for losses.

Patient data were recorded on a pre-coded structured questionnaire. Data on diagnosis, treatment and retreatment were extracted from routine registers.

The Institutional Research Board of the National Hospital for Tuberculosis and Respiratory Diseases in Hanoi gave scientific and ethical clearance for the study. Patients identified as smear- or culture-positive at follow-up were offered retreatment.

Data were collected by especially trained district TB staff and supervised by provincial staff. In addition, one of the authors (MV) supervised the data collection in 13 districts (41%). In November and December 2004, the selected patients were invited to the district unit. Patients who did not report were visited at their homes. If patients could not be found or had died, a non-response interview was completed with a family member. After written informed consent was obtained, one on-the-spot sputum sample was collected from each patient before and one after the interview.

Sputum smear microscopy and mycobacterial culture were performed at two provincial TB laboratories and the National Tuberculosis Reference Laboratory (NTRL) in Hanoi. Sputum specimens were transferred to the laboratory within 2 days after collection and examined using the Ziehl-Neelsen (ZN) method. For each patient, a single mycobacterial culture was performed on Ogawa medium using the simple decontamination method (i.e., without centrifugation) [11]. *Mycobacterium tuberculosis* was identified using the niacin test. Drug susceptibility testing (DST) was performed at the NTRL by the proportion method [12]. All

negative slides of patients with positive cultures and all positive slides of patients with negative cultures were reread by technicians blinded to the original results. Twenty per cent of slides were randomly selected and reread at the NTRL. When false negative results were detected from one laboratory, all slides from that laboratory were reread and the final results were based on the rereading.

A case was defined as smear-positive if at least one sputum smear examination was positive. A relapse case was defined as a patient who was smear- or culture positive at the time of follow-up or had been diagnosed with smear-positive TB and started retreatment in the interval between completion of initial treatment and time of follow-up.

*Analysis*

Data were double-entered using Epi Info 2002 (Centers for Disease Control and Prevention, Atlanta, GA, USA). Inconsistencies were checked against raw data. Data were analysed using SPSS 11.5 (SPSS Inc, Chicago, IL, USA). Two-sided Fisher's exact test or $x^2$ test was used to assess differences at the 5% significance level. $x^2$ test was used to test for aggregation of relapse by district.

## RESULTS

Included in the cohort were 304 patients. No information was available for 31 (10%) patients, of whom 17 had moved. Nineteen patients had died (6%). Of 254 patients available for follow-up (84%), interview data could be obtained for 253 and bacteriology results for 244 (Figure). Complete data were available for 243 (80%) patients. The median time interval between end of treatment and follow-up was 19.4 months (interquartile range [IQR], 17–22 months).

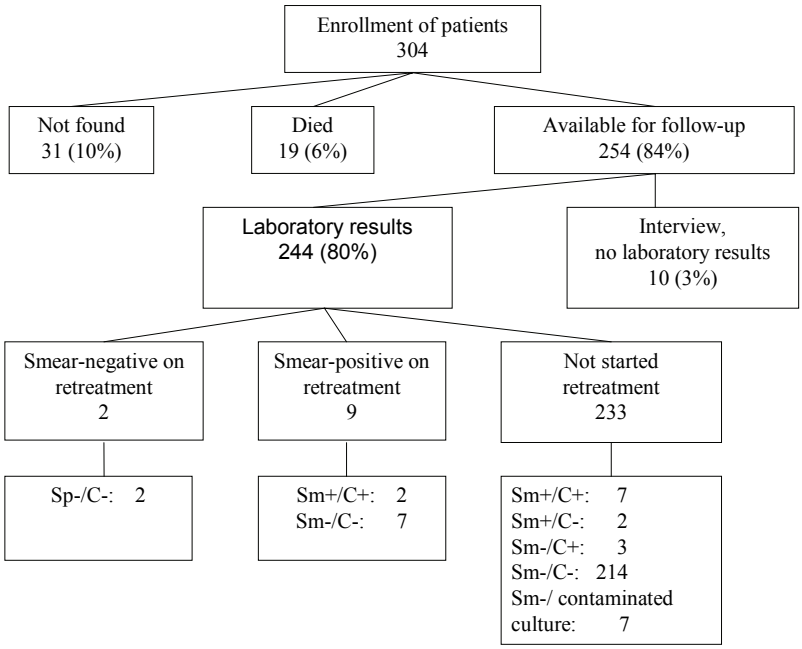
Baseline characteristics of patients are described in Table 1. Eleven patients (4%) had a negative HIV status as reported in the treatment register; HIV status was unknown for the remaining patients.

At the time of follow-up, 14 patients were smear or culture-positive (5.7%, 95% CI 3.2–9.5). Of these, 12 were not on retreatment, including 2 who were smear-positive, 3 who were culture-positive, and 7 who were both (Figure). Nine patients had started retreatment for smear-positive TB between the end of initial treatment and follow-up, of whom 2 were smear- and culture-positive and 7 smear- and culturenegative at the time of follow-up. The median interval between end of treatment and start of retreatment was 8 months (IQR 4–9 months). Of 12 strains isolated, 7 were resistant to any drug (58%, 95% CI 28–85), 6 to SM (50%, 95% CI 21–79) and 4 to both INH and RMP (MDR) (33%, 95% CI 10–65) (Table 2).

A total of 21/244 (8.6%, 95% CI 5.4–13) patients with bacteriology results had relapsed (sputum smear or culture-positive or started on retreatment). Relapse showed no significant aggregation by district ($p=0.22$). The proportion of relapses did not differ between patients with an interval from end of treatment to relapse or follow-up of 12–18 months and those

with an interval of >18 months (p=0.75). The proportion of relapses did not differ significantly by age, sex or area (Table 1), and was not associated with marital status, ethnicity, education level or indicators for socio-economic status or distance to the district TB unit (results not shown).

**Figure Study outcomes at time of follow-up of TB patients who successfully completed treatmen. TB = tuberculosis; Sm = smear; C = culture; - = negative; + = positive.**




For the 19 patients who had died, the median interval between end of treatment and death was 6 months (IQR 3–7 months), reported causes of death were TB or lung disease for 5 patients, other for 9 (including one patient with HIV/acquired immunodeficiency syndrome [AIDS]) and unknown for five. Mortality was significantly higher among patients aged ≥55 years (Table 1).

If the definition of relapse was extended to include death, reportedly due to TB, the relapse rate was 26/263 (9.9%, 95% CI 6.6–14). If all deaths were included, the relapse rate was 40/263 (15%, 95% CI 11–20).

The proportion of unfavorable outcomes (relapse or death) increased with age: 20% of patients aged ≥55 years had died or relapsed compared to 7% among those aged 15–34 (p=0.05).

**Table 1. Characteristics of TB patients who successfully completed treatment by relapse and survival at time of follow-up**

| | | Relapse | | | Survival | | |
|---|---|---|---|---|---|---|---|
| | n | Relapse n (%) | No relapse n (%) | p value | Death n (%) | Survived n (%) | p value |
| Total | 304 | 21 ( 9) | 223 (91) | | 19 (7) | 254 (93) | |
| Treatment outcome | | | | | | | 0.17 |
| Cured | 291 | 21 (9) | 215 (91) | 1 | 17 (6) | 245 (94) | |
| Completed | 13 | 0 | 8 | | 2 (18) | 9 (82) | |
| Age, years | | | | 0.21 | | | 0.024 |
| 15-34 | 58 | 1 (2) | 40 (98) | | 2 (4) | 44 (96) | |
| 35-54 | 115 | 10 (10) | 88 (90) | | 3 (3) | 103 (97) | |
| ≥55 | 131 | 10 (10) | 95 (90) | | 14 (12) | 107 (88) | |
| Sex | | | | 0.82 | | | 0.81 |
| Male | 196 | 14 (9) | 139 (91) | | 13 (7) | 162 (93) | |
| Female | 108 | 7 (8) | 84 (92) | | 6 (6) | 92 (94) | |
| Area | | | | 0.40 | | | 0.25 |
| Urban | 69 | 4 (9) | 42 (91) | | 4 (7) | 56 (93) | |
| Mountainous or remote | 97 | 9 (12) | 65 (88) | | 9 (11) | 75 (89) | |
| Rural | 138 | 8 (7) | 115 (93) | | 6 (5) | 123 (95) | |
| Follow-up sputum smear at 2 months | | | | 0.46 | | | 0.46 |
| Positive | 8 | 1 (17) | 5 (83) | | 1 (14) | 6 (86) | |
| Negative | 270 | 20 (9) | 195 (91) | | 15 (6) | 225 (94) | |
| No information | 26 | 0 | 23 | | 3 | 23 | |

TB = tuberculosis.

## DISCUSSION

Nine per cent of patients had relapsed within 12 to 24 months after ending TB treatment. Six per cent of TB patients who successfully completed treatment died.

Our estimate of the actual relapse rate is 9.9% (relapse cases and deaths due to TB), with a minimum of 7.7% (21 relapse cases out of 273 patients with known study outcomes). This minimum estimate assumes that all deceased patients died because of reasons other than TB and sputum could not be produced by the patients available for follow-up without collection of sputum samples, because they had no TB. The maximum relapse rate may be as high as 15%, if all deaths were due to TB.

**Table 2. Drug susceptibility of TB patients who successfully completed treatment and with culture-positive strains at time of follow-up (n = 12)**

| | *n* |
|---|---|
| Fully susceptible | 5 |
| Resistant to | |
| S | 2* |
| HS | 1 |
| HRS | 1 |
| HER | 1 |
| HRES | 2* |

*One patient on retreatment regimen
TB=tuberculosis; S= streptomycin; H= isoniazid;
R= rifampicin; E= ethambutol.

The estimated relapse rate in this study is a combination of true relapses who were smear- and culture negative at the end of treatment, and missed treatment failures. Missed treatment failures are cases who are not bacteriologically cured despite a negative smear (cure) or with no smear examination at the end of treatment (treatment completed). Although some may self-heal, most will develop overt smear-positive relapse over a period of several months [2]. These cases will be diagnosed and treated again, remain undiagnosed but survive for a prolonged period, or die.

The sum of the estimated relapse rate in this study and the reported failure rate of 0.4% in northern Vietnam in 2002 was similar to the combined failure and relapse rate of 10% in a randomized controlled trial among new smear-positive TB patients treated with 2EHRZ/6HE detected by active follow-up at 12 months after treatment completion [3]. The combined failure and relapse rate in northern Vietnam is therefore not in excess of what is expected based on this clinical trial.

Nevertheless, the relapse rate of around 10% observed in our study is substantial. Apart from an underestimated reported failure rate due to examination by smear microscopy instead of by the more sensitive culture method [6], several other causes may explain this. Drug intake during the continuation phase of treatment may have been irregular, as this is a risk factor for relapse [7], and in Vietnam the continuation phase is self-administered. With the regimen used, initial drug resistance to INH and/or SM predisposes to relapse [13]. In our study, pretreatment drug resistance data were not collected, but in a representative survey in 1996, prevalence among new smear-positive patients in northern Vietnam was 17%, 19% and 1.1% for INH, SM and MDR, respectively [9]. Of the culture positive relapse cases, 33% had MDR strains, i.e., significantly more than among new cases. Most importantly, the standard treatment regimen in Vietnam does not contain RMP in the continuation phase. In the randomized controlled trial mentioned, the relapse rate for a 6-month regimen containing RMP throughout (2ERHZ/4HR) was half (5%) that for

2ERHZ/6HE [3]. Therefore, changing from the current standard regimen to one with RMP in the continuation phase could reduce the relapse rate. However, there may be disadvantages to such a change. A treatment regimen containing RMP in the continuation phase, especially if the drug intake is unsupervised, may result in more MDR relapse cases than the 8-month regimen. Moreover, data from Ho Chi Minh City [14] suggest that a 6-month regimen that contains SM instead of EMB in the intensive phase has higher failure rates, probably related to the high initial resistance to SM and INH [15]. Of new patients in northern Vietnam in 1996, 7.7% had strains resistant to both INH and SM [9], and three of four relapse patients with MDR in this study also had SM resistance.

The mortality rate was high for patients who successfully completed TB treatment. This is likely due to the relatively old age of the patients in the cohort, as mortality was 12% among patients aged ≥55 years compared to 3% among those aged <55 years. This high mortality rate may be caused in part by TB. The cause of death was TB or lung disease for 5 (of 19) patients. However, the cause of death as reported by family members is probably not accurate, and the mortality rate attributed to TB can be under- or overestimated.

The relapse rate may have been overestimated. Since no DNA fingerprinting was performed of *M. tuberculosis* strains before treatment and at relapse, we could not distinguish between relapse and re-infection [2].

At the time of follow-up, nine patients had started retreatment and nine were smear-positive and had not yet started retreatment. One consequence of this high relapse rate is therefore that early case finding of relapsed patients should be considered. Another consequence is that this high relapse rate may contribute substantially to continued transmission, in particular of multidrug-resistant TB.

Interventions to lower the relapse rate and deaths due to TB should be investigated for cost-effectiveness, such as confirmation of cure by culture, supervision of drug intake during the continuation phase or a change in the treatment regimen.

## CONCLUSION

A substantial proportion of patients (15%) had died or relapsed after being successfully treated with the 8-month TB treatment regimen in northern Vietnam.

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# Chapter 8

# Anti-tuberculosis drug resistance in the south of Vietnam: Prevalence and trends

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**ABSTRACT**

*Background:* There is limited evidence that the DOTS (directly observed therapy, short course) Strategy for tuberculosis (TB) control can contain the emergence and spread of drug resistance in the absence of second-line treatment. We compared drug-resistance levels between 1996 and 2001 in the south of Vietnam, an area with a well-functioning DOTS program.

*Methods:* Sputum specimens were collected from consecutively diagnosed patients with smear-positive TB at 40 randomly selected public TB clinics. *Mycobacterium tuberculosis* isolates were tested for susceptibility to first line drugs.

*Results:* Among 888 new patients in 2001, resistance to any drug was observed in 238 (26.3%), resistance to isoniazid was observed in 154 (16.6%), resistance to rifampin was observed in 22 (2.0%), resistance to ethambutol was observed in 12 (1.1%), resistance to streptomycin was observed in 173 (19.4%), and resistance to both isoniazid and rifampicin (multidrug resistance [MDR]) was observed in 20 (1.8% [95% confidence interval, 1.0%–3.3%]). Among 136 previously treated patients in 2001, any resistance was observed in 89 (62.9%), and MDR was observed in 35 (23.2%). The prevalence of any drug resistance and of streptomycin resistance among new patients had decreased significantly ($p<0.01$) since 1996; there was no increase in the prevalence of MDR.

*Conclusion:* The prevalence of drug resistance decreased despite high initial levels of resistance to isoniazid and streptomycin and despite the absence of second-line treatment. Therefore, a DOTS program can contain drug resistant TB in this setting.

## INTRODUCTION

With >8 million cases and 2 million deaths annually, tuberculosis (TB) is a major cause of morbidity and mortality worldwide [1]. The approach to TB control advocated by the World Health Organization (WHO) is DOTS (directly observed therapy, short course), which focuses on the treatment of sputum smear–positive pulmonary TB with standardized short-course chemotherapy under proper case-management conditions [2].

Among the objectives of the DOTS Strategy is the prevention of the emergence and spread of resistance to anti-TB drugs, in particular of resistance to both isoniazid and rifampin (multidrug resistance [MDR]). MDR-TB carries a highly increased risk of treatment failure or death with short-course chemotherapy and is an important challenge for TB control [3–5]. An increasing number of TB control programs are adding second-line treatment of patients with MDR-TB to their DOTS services (previously called "DOTS-Plus") [6]. Although it is clear that the individual patient with MDR-TB benefits from second-line treatment [7], it is still a matter of debate whether and under what conditions the DOTS Strategy as such is effective in containing the spread of drug resistance [8]. Recently, a prospective population-based study in Mexico showed that the introduction of DOTS rapidly reduced the transmission and incidence of drug-resistant TB [9]. In Botswana, however, repeated nationwide surveys showed a significant increase in the prevalence of drug resistance among new patients with TB, despite the presence of a long-standing DOTS program [10].

Vietnam is among the countries with a high burden of TB [6]. The National Tuberculosis Control Program of Vietnam (NTPV) implemented the DOTS Strategy in 1989, and the estimated case-detection rate has been 70% since 1997 [6,11]. The NTPV's standard treatment regimen for new (i.e., previously untreated) patients consists of 2 months of streptomycin, isoniazid, rifampin, and pyrazinamide, followed by 6 months of isoniazid and ethambutol (the 2SHRZ/6HE regimen). It has been used widely since 1990, with cure rates well over 85% and failure rates <3% [11].

Despite high performance by these indicators, there are concerns about the ability of the NTPV to control the spread of drug resistance in the absence of second-line treatment [12]. This applies in particular to the southern part of the country, which in 2002 was home to 38% of the country's population of 80 million but carried 54% of the burden of smear-positive TB [11]. In the first nationwide drug-resistance survey conducted among new patients with smear-positive TB in 1996, this region had the highest level of drug resistance (36.1%) [13]. In particular, the levels of resistance against isoniazid (21.6%) and streptomycin (29.4%) were high, as was the level of MDR (3.5%). Subsequent studies of new patients with smear-positive TB in Ho Chi Minh City showed that 15 (65.2%) of 23 patients who experienced treatment failure during the 2SHRZ/6HE regimen developed MDR-TB and that the risk of treatment failure for those infected with strains resistant to both streptomycin and isoniazid was increased 13-fold, compared with that for those infected with pansusceptible strains [14,15]. Moreover, the south of Vietnam has a rapidly expanding private health sector, in particular in the large urban area of Ho Chi Minh City. It

has been estimated that 30%–40% of all TB cases in Ho Chi Minh City are treated in the private sector [16], with low cure rates [17,18].

As part of the WHO/International Union against Tuberculosis and Lung Disease (IUATLD) Global Project on Drug-Resistance Surveillance, the NTPV conducted a second nationwide survey of anti-TB drug resistance among new patients with smear-positive TB in 2001. This survey also included previously treated patients. Here, we report the results for the south of Vietnam and compare them with the results from the previous survey, to assess trends over time.

## METHODS

The survey was conducted between 1 August and 31 October 2001 in 40 clusters (i.e., district TB units, general hospitals, and designated TB hospitals). These included the 22 clusters studied in the 1996 survey, which had been randomly selected in 1995 with sampling probabilities proportional to the number of notified new patients with smear-positive TB in 1994. The 18 clusters added to these were randomly selected in 2001 with sampling probabilities proportional to the number of notified new patients in 2000. In each cluster, 23 consecutively registered new patients with smear-positive TB were enrolled.

To obtain information on the level of acquired drug resistance, each cluster was requested to also submit sputum specimens from each consecutive patient with smear-positive TB who had a history of TB treatment for 1 month or more and had received their diagnosis during the period in which the new patients were included. This was expected to be 4 patients/cluster, on average. Among the clusters selected for the first survey were 3 that had each been administratively split into 2 clusters since the first survey was conducted but were inadvertently treated as multiple clusters in the data-collection process. In the analysis, these were treated as single clusters, with consequently larger numbers of patients.

Two sputum specimens were collected from each patient and sent, without the addition of decontaminant, to the Regional Mycobacterial Reference Laboratory (RMRL) in HoChiMinh City within 4 days. Treatment history and symptoms were ascertained by clinic staff from treatment registers and by interviewing the patient by means of a standard questionnaire.

At the RMRL, specimens were decontaminated and homogenized with 4% NaOH, inoculated onto modified Ogawa medium by the Petroff method, and incubated at 35°C–37°C for up to 4–8 weeks [19]. Cultures were examined for growth at the end of weeks 1, 2, 4, 6, and 8 after inoculation; cultures with no growth after 8 weeks were reported as negative. *Mycobacterium tuberculosis* was identified by the niacin test. Drug susceptibility testing (DST) was done by the proportion method, in accordance with WHO/IUATLD guidelines [19]. Criteria for drug resistance were ≥1% colony growth at 28 or 40 days relative to the drug-free control medium at the following drug concentrations: for isoniazid, 0.2 mg/mL; for rifampin, 40 mg/mL; for streptomycin, 4 mg/mL; and for ethambutol, 2 mg/mL [19]. External DST quality control was done by annual proficiency testing

undertaken by the Supranational Reference Laboratory in Seoul, South Korea. Concordance in 2001 was 100% for both isoniazid and rifampin and was 93% for both streptomycin and ethambutol.

**Table 1. Patterns of drug resistance among patients with smear-positive pulmonary tuberculosis in the south of Vietnam, 2001.**

| Drug resistance pattern | No. (% [95% CI]) New patients (n = 888) | | No. (% [95% CI]) Previously treated patients (n = 136) | |
|---|---|---|---|---|
| Sensitive to all 4 drugs | 650 | (73.8 [69.6-77.5]) | 47 | (37.1 [26.9-48.6]) |
| Any resistance | 238 | (26.3 [22.5-30.4]) | 89 | (62.9 [51.4-73.1]) |
| Any resistance to : | | | | |
| H | 154 | (16.6 [13.9-19.6]) | 70 | (52.0 [39.9-63.8]) |
| R | 22 | (2.0 [1.1-3.6]) | 40 | (26.3 [16.4-39.3]) |
| E | 12 | (1.1 [0.5-2.6]) | 15 | (9.1 [0.4-21.1]) |
| S | 173 | (19.4 [16.1-23.3]) | 64 | (38.8 [28.0-50.7]) |
| Monoresistance to : | | | | |
| H | 59 | (6.3 [4.7-8.3]) | 15 | (15.4 [8.5-26.3]) |
| R | 1 | (0.1 [0-0.7]) | 4 | (2.0 [0.7-5.7]) |
| E | 0 | (0) | 0 | (0) |
| S | 82 | (9.5 [7.3-12.2]) | 14 | (7.9 [4.5-13.3]) |
| Total | 142 | (15.9 [12.9-19.3]) | 33 | (25.3 [16.7-36.4]) |
| Multidrug resistance | | | | |
| HR | 4 | (0.4 [0.1-1.0]) | 4 | (4.9 [1.6-14.3]) |
| HRE | 1 | (0.1 [0-0.6]) | 1 | (1.1 [0.2-7.6]) |
| HRS | 8 | (0.8 [0.4-1.6]) | 18 | (11.1 [5.7-20.6]) |
| HRES | 7 | (0.6 [0.2-2.3]) | 12 | (6.1 [2.5-14.2]) |
| Total | 20 | (1.8 [1.0-3.3]) | 35 | (23.2 [13.6-36.8]) |
| Other patterns | | | | |
| HE | 0 | (0) | 1 | (0.7 [0.1-4.9]) |
| HS | 71 | (8.0 [6.0-10.8]) | 18 | (11.4 [6.9-18.5]) |
| HES | 4 | (0.5 [0.2-1.4]) | 1 | (1.2 [0.2-8.1]) |
| RS | 1 | (0.1 [0-0.8]) | 1 | (1.0 [0.1-7.2]) |
| Total | 76 | (8.6 [6.5-11.3]) | 21 | (14.4 [8.8-22.7]) |

Note. Percentage shown are weighted for individual sampling probabilities. CI = confidence interval; H = isoniazid, R = rifampin, E = ethambutol, S = streptomycin.

Data were double entered into EpiInfo (version 6.4; Centers for Disease Control and Prevention), and discrepancies were checked against the raw data. Data were analyzed in Stata (version 8; StataCorp). Isolates identified as *mycobacteria* other than TB (MOTT) were excluded from the analysis.

Drug resistance among new patients was defined as the presence of resistant *M. tuberculosis* isolates in newly diagnosed patients who either had never been treated with anti-TB drugs or had been treated for <1 month. Drug resistance among previously treated patients was defined as that found in patients with a history of a least 1 month of anti-TB therapy. Multidrug resistance was defined as resistance to at least isoniazid and rifampin [19].

The prevalence of drug resistance was calculated as the proportion across all clusters after weighting for the exact sampling probabilities for each individual patient for whom DST results were available. Although the sampling scheme was intended to be self-weighting, this weighed analysis was preferred for 2 reasons. First, the sampling probabilities of the clusters selected in 1994 differed from the probabilities by which these clusters would have been sampled in 2000. Second, there was large variation in the numbers of patients for whom DST results were available. The exact sampling probabilities were calculated as the cluster sampling probability times the individual sampling probability within the cluster. The cluster sampling probabilities were calculated as the cluster patient load times the number of selected clusters divided by the total patient population, using data for the year 1994 for clusters that had been selected for the first survey and data for the year 2000 for clusters that were selected for the second survey only. Individual sampling probabilities were calculated as the number of patients for whom DST results were obtained divided by the cluster patient load in 2000. In all these analyses, confidence intervals (CIs) and p values were adjusted for the cluster design by first order Taylor linearization and by the second-order correction of Rao and Scott of the Pearson $x^2$ test, respectively, as implemented by the Stata svy commands [20, 21].

Multivariate analysis was done by logistic regression. Because population weights were applied, p values were based on the Wald statistic [22]. For age group, the p values presented are for ordinal linear fitting.

For comparison with the previous survey, design effects were calculated separately for the 2 surveys. Aggregation of MDR-TB cases within clusters was analyzed by assessing the intraclass coefficient r by 1-way analysis of variance [23].

**RESULTS**

During the study period, 2 360 sputum specimens were collected from 1 180 patients with smear-positive pulmonary TB. On the basis of an expected number of 23 new patients for each cluster, the proportion of specimens received at the RMRL was 106%. Specimens from <23 patients were received from 19 clusters (47.5%), including 4 (10.0%) with 15 or less, primarily because of insufficient numbers of patients registered during the inclusion period. Excluded were 118 patients (10%) because of either culture contamination (9 patients [1%]), negative culture result (98 patients [9%]), or growth of MOTT (11 patients

**Table 2. Risk factors associated with any isoniazid, streptomycin and multidrug resistance among new patients with smear-positive pulmonary tuberculosis in 2001-2002.**

| Risk factor | Proportion (%) | OR (95% CI) crude | OR (95% CI) Adjusted | p |
|---|---|---|---|---|
| **Any isoniazid resistance** | | | | |
| Residence | | | | 0.009 |
| Rural | 105/670 (14.5) | 1 | 1 | |
| Urban | 49/218 (22.4) | 1.70 | 1.68 (1.14-2.47) | |
| Sex | | | | 0.606 |
| Males | 115/642 (17.3) | 1 | 1 | |
| Females | 39/246 (14.6) | 0.82 | 0.87 (0.52-1.47) | |
| Age group | 21/ 92 (17.4) | 1 | 1 | 0.569 |
| 15-24 yeas | 32/184 (15.1) | 0.84 | 0.84 (0.42-1.69) | |
| 25-34 yeas | 45/223 (21.8) | 1.32 | 1.32 (0.69-2.53) | |
| 35-44 yeas | 20/153 (12.5) | 0.68 | 0.70 (0.35-1.39) | |
| 45-54 yeas | 14/102 (14.8) | 0.83 | 0.92 (0.39-2.21) | |
| 55-64 yeas | 21/130 (13.7) | 0.75 | 0.87 (0.47-1.61) | |
| 65+ yeas | | | | |
| **Any streptomycin resistance** | | | | |
| Residence | | | | 0.002 |
| Rural | 111/670 (16.0) | 1 | 1 | |
| Urban | 62/218 (29.2) | 2.15 | 2.01 (1.29-3.12) | |
| Sex | | | | 0.198 |
| Males | 111/642 (18.3) | 1 | 1 | |
| Females | 62/246 (22.2) | 1.27 | 1.35 (0.85-2.13) | |
| Age group | | | | 0.024 |
| 15-24 yeas | 26/ 92 (25.3) | 1 | 1 | |
| 25-34 yeas | 37/184 (19.7) | 0.73 | 0.81 (0.37-1.77) | |
| 35-44 yeas | 44/223 (22.4) | 0.85 | 0.99 (0.44-2.25) | |
| 45-54 yeas | 32/153 (18.5) | 0.67 | 0.79 (0.38-1.65) | |
| 55-64 yeas | 16/102 (20.6) | 0.77 | 0.97 (0.42-2.23) | |
| 65+ yeas | 18/130 (10.5) | 0.35 | 0.44 (0.21-0.94) | |
| **Multidrug resistance** | | | | |
| Residence | | | | 0.615 |
| Rural | 15/670 (1.6) | 1 | 1 | |
| Urban | 5/218 (2.2) | 1.34 | 1.32 (0.45-3.88) | |
| Sex | | | | 0.096 |
| Males | 16/642 (2.0) | 1 | 1 | |
| Females | 4/246 (1.2) | 0.57 | 0.41 (0.14-1.18) | |
| Age group | | | | 0.572 |
| 15-24 yeas | 4/ 92 (4.6) | 1 | 1 | |
| 25-34 yeas | 6/184 (2.1) | 0.43 | 0.36 (0.09-1.47) | |
| 35-44 yeas | 2/223 (0.5) | 0.10 | 0.08 (0.01-0.53) | |
| 45-54 yeas | 2/153 (1.2) | 0.25 | 0.21 (0.03-1.27) | |
| 55-64 yeas | 3/102 (2.5) | 0.54 | 0.50 (0.11-2.32) | |
| 65+ yeas | 3/130 (1.9) | 0.41 | 0.40 (0.11-1.53) | |

Note. Percentage shown are weighted for individual sampling probabilities. Crude and adjusted odds ratios (ORs) are based on logistic regression analysis. Adjusted ORs are adjusted for all other variables in the model. P-values are based on the likelihood ratio $\chi^2$ test. CI = confidence interval.

[1%]). Previous treatment status was missing for 38 patients (3%). The remaining isolates from 1024 patients (87%) underwent DST. Of 1024 strains, 888 (87%) were isolated from new patients, and 136 (13%) were isolated from previously treated patients.

The mean number of new patients per cluster was 22 (range, 5–40). Of the 888 isolates from new patients, 238 (26.3%) were resistant to at least 1 drug, 154 (16.6%) were resistant to isoniazid, 22 (2.0%) were resistant to rifampin, 12 (1.1%) were resistant to ethambutol, 173 (19.4%) were resistant to streptomycin, and 20 (1.8%) were MDR (resistant to both isoniazid and rifampin) (Table 1). There were 9 clusters with 1 MDR case, 2 clusters with 2 MDR cases, 1 cluster with 3 MDR cases, and 1 cluster with 4 MDR cases.

The distribution of MDR isolates among clusters showed no significant aggregation ($\rho$=0.03 [95% CI, 0–0.06]). Of the 20 MDR isolates, 7 (35.0%) were resistant to isoniazid, rifampin, streptomycin, and ethambutol, and 8 (40.0%) were resistant to isoniazid, rifampin, and streptomycin.

Of the 136 isolates from previously treated patients, 89 (62.9%) were resistant to at least 1 drug, 70 (52.0%) were resistant to isoniazid, 40 (26.3%) were resistant to rifampin, 15 (9.1%) were resistant to ethambutol, and 64 (38.8%) were resistant to streptomycin (table 1). MDR was observed in 35 isolates (23.2%) and aggregated significantly within clusters ([95% CI, 0.12–0.51]). There were 10 clusters $\rho$=0.32 with 1 MDR case, 1 cluster with 2 MDR cases, 3 clusters with 3 MDR cases, 2 clusters with 4 MDR cases, and 1 cluster with 6 MDR cases.

Both isoniazid and streptomycin resistance in new patients was significantly more common in urban areas than in rural areas (adjusted odds ratio [aOR] for isoniazid resistance, 1.68 [95% CI, 1.14–2.47]; aOR for streptomycin resistance, 2.01 [95% CI, 1.29–3.12]) (Table 2). Resistance to streptomycin was significantly associated with age, whereas resistance to isoniazid was not. The prevalence of resistance to streptomycin was significantly lower among patients ≥65 years old than among younger patients (p=0.024). MDR was not associated with age, sex, or urban/rural residence (Table 2).

Comparison of the results of the second survey (2001) with those of the first (1996) showed a significant decrease in the prevalence of resistance to any drug (from 36.1% to 26.3%; $p<0.01$) and of resistance to streptomycin (from 29.4% to 19.4%; $p<0.01$) among new patients. The prevalence of MDR also decreased (from 3.5% to 1.8%) during this period, but the difference was not significant (Table 3).

Repetition of the analysis without weighting for individual sampling probabilities for new patients in the 2001 survey changed the prevalence estimates for any resistance (26.8%), for streptomycin resistance (19.5%), and for MDR (2.3%) by 0.5% or less. It did not affect the results of the comparison with the 1996 survey.

**Table 3. Prevalence of drug resistance among new patients with smear-positive pulmonary tuberculosis in 2001-2002 compared to 1996-1997 in the South of Vietnam**

| | No. (%) | | | |
|---|---|---|---|---|
| Drug resistance pattern | 1996-97 (n = 374) | | 2001-02 (n = 888) | | p |
| Sensitive to all 4 drugs | 239 | (63.9) | 650 | (73.7) | <0.01 |
| Resistance to any drug | 135 | (36.1) | 238 | (26.3) | <0.01 |
| Any resistance to : | | | | | |
| H | 81 | (21.6) | 154 | (16.6) | >0.05 |
| R | 17 | (4.5) | 22 | (2.0) | >0.05 |
| E | 5 | (1.3) | 12 | (1.1) | >0.05 |
| S | 110 | (29.4) | 173 | (19.4) | <0.01 |
| Monoresistance to : | | | | | |
| H | 20 | (5.3) | 59 | (6.3) | >0.05 |
| R | 3 | (0.8) | 1 | (0.1) | >0.05 |
| E | 0 | | 0 | | >0.05 |
| S | 50 | (13.4) | 82 | (9.5) | >0.05 |
| Total | 73 | (19.5) | 142 | (15.9) | |
| Multi drug resistance | 13 | (3.5) | 20 | (1.8) | >0.05 |
| HR | 2 | (0.5) | 4 | (0.4) | >0.05 |
| HRE | 0 | | 1 | (0.1) | >0.05 |
| HRS | 6 | (1.6) | 8 | (0.8) | >0.05 |
| HRES | 5 | (1.3) | 7 | (0.6) | >0.05 |
| Total | 13 | (3.5) | 20 | (1.8) | >0.05 |
| Other patterns | 49 | (13.1) | 76 | (8.6) | >0.05 |
| HS | 48 | (12.8) | 71 | (8.0) | >0.05 |
| HES | 0 | | 4 | (0.5) | >0.05 |
| RS | 1 | (0.3) | 1 | (0.1) | >0.05 |
| Total | 49 | (13.1) | 76 | (8.6) | >0.05 |

Note. Percentages shown for 2001 are weighted for individual sampling probablities. p-values based on $\chi^2$ test with continuity correction of 2-sided Fisher's exact test for comparison between two survey periods. H = isoniazid, R = rifampin, E = ethambutol, S = streptomycin.

**DISCUSSION**

In the south of Vietnam, the prevalence of drug resistance among new patients with smear-positive TB decreased during the period 1996–2001. The prevalence of MDR-TB also declined, but the decrease was not significant. These findings indicate that the NTPV has managed to contain the emergence and spread of drug resistance, including MDR, and are consistent with the high cure rates (88.0% in 1996 and 91.8% in 2001) and low failure rates (1.7% in 1996 and 1.3% in 2001) reported for this part of the country (NTPV, unpublished data). This containment has been achieved by a DOTS program that does not include second-line treatment of patients with MDRTB and in spite of several challenges to effective TB control: high levels of initial drug resistance to isoniazid and streptomycin [13], an increasing contribution to TB treatment from the private sector [16–18], and the spread of new *M. tuberculosis* strains, such as the Beijing genotype [24].

The decrease in the prevalence of drug resistance since 1996 predominantly reflected a decrease in resistance to streptomycin. This could be due to a natural decrease in the number of patients with reactivation TB who had been infected a long time ago when the uncontrolled use of streptomycin and isoniazid was widespread. However, initial resistance to streptomycin was least frequent in the oldest age group and most frequent in the youngest, suggesting a different explanation. One may be the role played by strain genotype. In a study of *M. tuberculosis* isolates mainly from the south of Vietnam, the Beijing genotype was associated both with drug resistance (notably to streptomycin) and with younger age, suggesting recent transmission [24]. Thus, recent selection and spread of Beijing strains could have resulted in a relative increase in the prevalence of streptomycin resistance that partly compensated for the decreasing prevalence due to the ageing of the patient population infected with streptomycin-resistant strains before 1975. Studies are under way to further explore the association between age, drug resistance, and genotype in Vietnam. Initial resistance to isoniazid and streptomycin was also more common in urban areas. This may reflect differences in the availability of these drugs on the free market and in the contribution of private health providers to TB treatment.

In the 1996 survey, resistance among previously treated patients was not assessed. In the 2001 survey, nearly two-thirds of the previously treated patients were infected with strains that were resistant to at least 1 drug, and nearly one-quarter were infected with MDR strains. Similar resistance levels were observed in recent studies in HoChiMinh City [14,15]. The levels are consistent with high treatment adherence (i.e., a large proportion of patients who experienced treatment failure did so because of initial drug resistance) but also with the amplification of drug resistance via use of the 2SHRZ/6HE regimen in the presence of high initial levels of isoniazid and streptomycin resistance [12,15].

There are limitations to the present study. First, previous treatment of TB may have been missed—that is, previously treated patients may have been misclassified as new patients. (The opposite, new patients being misclassified as previously treated patients, may also have occurred but is less probable). The effect would be overestimation of drug resistance among new patients. However, a substantial effect on the trend estimates would be unlikely,

because the proportion of previously treated patients reported by the NTPV has remained constant since 1995 [11].

Second, the inclusion of part of the same clusters surveyed in 1996 and the variation in the numbers of specimens that were available for DST were reason for use of a weighed analysis based on individual sampling weights. Although in our view this analysis provides the best estimate from the available data, it is influenced by clusters from which only a few specimens were tested. Although this had only a minimal effect on the estimates of the prevalence of drug resistance, it may have affected the representativeness of our survey sample.

We conclude that, in the south of Vietnam, the prevalence of drug resistance has significantly decreased and that levels of drug resistance, including MDR, among new patients with smear-positive TB have not increased during the past 6 years. This occurred despite high initial levels of resistance to isoniazid and streptomycin and despite the absence of second-line treatment. Although the availability of second-line treatment in a DOTS-Plus program is important from the perspective of an individual patient, a well-functioning DOTS program with high cure rates among new patients is apparently sufficient for containing MDR-TB in this setting.

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# Chapter 9

# General Discussion

The studies presented in this thesis focused on determining why a DOTS program in a high-burden country that meets the WHO targets of at least 70% case detection and at least 85% cure apparently failed to have an impact on TB transmission and disease burden.

**MAIN FINDINGS**

Vietnam is among 22 highest TB burden countries in the world. The NTP of Vietnam introduced DOTS Strategy in 1989 and achieved 100% DOTS coverage in 2000. The proportion of smear-positive cases detected and put on short-course treatment was over 70% since 1996. Reported cure rates with short-course chemotherapy are consistently over 85%. However, TB case notification rates in Vietnam show no decline (Chapter 2).

Total, patient and health care provider delays in TB diagnosis and treatment were short in Vietnam. Median delay was 4 weeks for total, 3 weeks for patient and 1 week for health care delay. Nonetheless, 15% of patients reported total delay ≥12 weeks, and accounted for 49% of the cumulative number of delay-weeks. Initial visit to the private sector had a considerable impact on the length of delays but with distinct regional differences across the country (Chapter 3).

In the north of Vietnam, 9.7 suspects were examined and 29.3 smears done to find one smear-positive case. The smear-positive rate was 10.3%. The male:female ratios were 1.36 among TB suspects and 1.89 among smear-positive patients, suggesting higher TB incidence among men rather than lower access to TB facilities for women (Chapter 4).

The overall annual notification rate of smear positive TB per 100,000 population was 78; 9 per 1,000 population had sputum smear examination. The case notification rates (CNR) were higher in the south and centre than in the north. Geographical variations in CNRs largely reflected true epidemiological differences in TB distribution in Vietnam. CNRs varied remarkably by latitude, zone and urbanity and were not associated with poverty or ethnicity at commune level. The distance to the district health center was a key factor determining access to TB services, suggesting under-diagnosis in areas further away from health facilities (Chapter 5).

In 6 sentinel provinces where the DOTS Strategy had been introduced in the 1980s, the CNRs of new smear-positive tuberculosis over the period 1996-2003 decreased by 2.5 to 5.9% per year in all provinces except HCMC. Over the same period, the ARTI decreased in 2 of 6 provinces by 6.6 to 14.7% per year. This suggests that control efforts are beginning to have impact on the tuberculosis epidemic in Vietnam. Over this period, however, the CNR in the youngest age group (15-24 years) in 4 provinces were found to increase by 4.5% to 13.6% per year, and to decrease less than average in the remaining two. As a result, the expected increase in the mean age of notified cases is not observed in the provinces studied. The increase in the younger age groups partly offsets stronger decreases in CNR in the other age groups. Thus, a new epidemic wave may be underway, in particular in HCMC where the CNR in the youngest age group increased by 13.6% per year (Chapter 6).

Among 304 patients included in the study in the northern part of the country, the bacteriology relapse rate was 5%. An additional 4% started TB retreatment. Four of 12 culture-positive relapse cases (33%) had multidrug-resistant strains. In total, the relapse proportion was 9.9% (Chapter 7).

In the south of Vietnam, among new patients, the prevalence of resistance to any drug was 26% and the prevalence of MDR 1.8%. Among previously treated patients, prevalence of any resistance and MDR was 63% and 23% respectively. The prevalence of resistance to any drug has significantly declined and the level of multidrug resistance among new smear-positive patients has not increased over the past six years in the absence of second-line treatment (Chapter 8).

In conclusion, national level data suggest that in Vietnam the DOTS Strategy is insufficient to reduce TB incidence, but detailed analysis of data from sentinel provinces indicate that there is in fact impact but the impact has been modest. The impact is less than predicted by models. The main explanation is an increase in CNR among young adults. The short average delay and the relatively low average smear-positive rate suggest that the case detection rate is at least not low. The findings suggest substantial variation in case detection rate between parts of the country and between subpopulations, as well as substantial variation in TB incidence. The relapse rate was not above that expected with the 8-month regimen used for the treatment of new TB patients. This and the stable or even partially declining drug resistance levels suggest that reported cure rates are not grossly overestimating true cure rates, and that the reported treatment efficacy is as expected with the standard first-line regimens used.

## MAJOR LIMITATIONS AND EXPLANATIONS

In this chapter possible explanations for the shortfall in decrease in TB notification rates in Vietnam are discussed, as well as a number of limitations to the data. It may be that the TB notification data in Vietnam are unreliable, i.e. do not reflect the true numbers of patients diagnosed; that despite our findings the true case detection rate in Vietnam is below the 70% target; and that the true cure rate is lower that reported. Additional explanations for the shortfall in decline in TB incidence may be grouped as reflecting increased rates of progression of *M. tuberculosis* infection to disease, or as increased rates of *M. tuberculosis* transmission (both compared to the rates assumed in prediction models).

### Reliability of routine surveillance data

The Vietnam National Tuberculosis Control Programme (NTP) has a very well developed registration, recording and reporting system as recommended by IUATLD and WHO [1]. All AFB microscopy centers keep laboratory registers to record suspects examined by direct microscopy. All district TB centers keep district TB registers in which patients are registered when started on treatment. The district reports of the results of case finding and treatment are submitted to the provincial/national level on a quarterly basis.

The reliability of the routine NTP data can be questioned for a number of possible reasons, including non-registration of diagnosed patients ("initial defaulting"), diagnostic misclassification, and the use of incentives and targets for reporting.

The NTP has collected routine data on initial defaulting – the situation in which patients diagnosed by the NTP with (smear-positive) TB are not registered for treatment and thus not notified - since 2001. The proportion of initial defaulters among new smear-positive patients in the period 2001-2005 was 2-6% [2]. A study in HCMC in 2000 showed that the proportion initial defaulting was 8.3% [3]. This may contribute to an underestimate of case notifications.

Diagnostic misclassification may occur due to false-negative or false-positive diagnostic smears, and to misclassification of treatment history. The NTP operates a well-developed external quality assurance system for smear examination [1] based on blinded rereading of all positive slides and 10% negative slides monthly at provincial laboratories [4]. The system found more than 99% concordance, 0.3% false negatives and 0.4% false positives among 151 719 positive and 186 435 negative slides reported for 2005 [2]. Misclassification of previously treated patients as new and vice versa may occur for various reasons including recall errors and insufficient history taking. Misclassification of retreatment cases as new is probably more common than vice versa. The proportion of smear-positive cases registered for retreatment remained stable after 1995 at around 10% (Chapter 1) [2]. These observations suggest that diagnostic misclassification may occur but is unlikely to have a major effect on the routine NTP reporting data.

Since 1996 the NTP has applied an incentive system for case detection and completion of TB treatment (Chapters 1, 2). For each patient detected with sputum smear-positive TB the health worker receives US$0.70, and for each completed course of TB treatment US$3.5 in lowland areas and US$7.5 in mountainous areas [5]. This may affect case notifications of new smear-positive TB.

The NTP sets annual targets for case detection and cure. These targets are using for planning, financing and ordering of drugs [2]. At provincial level, based on the national and provincial target, provinces set the target for districts for number of TB suspect, case detection and cure. This target system may work two ways: additional (active) case finding may be started when targets appear not to be met, and case finding efforts may become less if targets have been met before the end of the period. As for incentives, a tendency for meeting case finding and treatment outcome targets may affect reporting, but it is unlikely that such effect would be different for different age groups. Although they may have a "damping" effect on decreases in case notification in general, it is unlikely that incentives and targets are responsible for the observed rise in CNR among young adults.

**Accuracy of the case detection rate**

The data presented in this thesis on diagnostic delay, proportion of the population examined and smear-positive rate do not suggest that the CDR in Vietnam is low. However, these

data have limitations since they are indirect. In fact, how the average delay, suspect rate or smear-positive rate relates to the actual CDR is uncertain. In addition, there may be reasons to question the accuracy of the CDR as estimated for Vietnam.

The numerator for the case detection target is the number of new cases of sputum smear-positive tuberculosis registered in one year, and the denominator is the number of new sputum smear-positive cases estimated to have arisen in the same population over the same period [6]. As the case detection target relies on an estimate for the incidence of tuberculosis, it is difficult to measure it accurately in most settings.

In Vietnam, the estimated annual incidence of new smear positive TB was estimated based on a countrywide ARTI of 1.7% [7], with an estimate of approximately 50 incident sputum smear-positive cases for each 1% of annual risk of infection [8,9]. There are two problems which are the interpretation of tuberculin data and the correlation between TB incidence and ARTI.

Tuberculin surveys have various methodological problems including selection of standardized tuberculin, the technique of administration, and reading of the test results. Even if all of these barriers are overcome, it is in many circumstances difficult to arrive at an estimate of the prevalence of infection. Sensitization to environmental *mycobacteria* and *M.bovis* BCG results in cross-reactions with the standard tuberculin. The higher this sensitization is and the lower the prevalence of true infection with tubercle bacilli, the more difficult it becomes to disentangle the true prevalence from confounding factors [10]. Assuming that the prevalence of infection with *M. tuberculosis* has been satisfactorily estimated, the essence of the analysis of a tuberculin skin test survey is the estimation of the average annual risk of infection. The annual risk of infection refers to a risk at a specified calendar year. Estimates of the risk of infection were usually derived from surveys in a single age group, and have thus assumed a constant risk of infection across age groups. If the risk of infection varies considerably by age, extrapolations from a single age group might thus be erroneous [10,11].

In Vietnam, a countrywide ARTI of 1.7% was the average of the ARTI estimated from the sentinel tuberculin surveys done in different regions of the country in the period 1986-1994. It was estimated among children with no BCG and based on a definition of TB infection of any reaction size of 10mm or more. The results from the sentinel tuberculin surveys were not representative for the country as a whole. Estimates of the ARTI are obtained from tuberculin reaction size distributions among children without BCG scar. The proportion of children vaccinated with BCG has however increased over time. The children who had no BCG scar in the last round may thereby not be representative with respect to their risk of TB or the size of the tuberculin skin test response if infected. A substantial proportion of children, both with and without BCG scar, have intermediate size reactions that are probably due to cross-reaction to environmental mycobacteria. A cut-off of 10mm as criterion for TB infection may then overestimate the infection prevalence. There may be a north-south gradient in the mode of the distribution of reaction sizes among TB patients

from 19mm in the north to 15mm in the south. The result would be that the sensitivity of the 10 mm criterion also differs between provinces (Chapter 6).

One per cent risk of infection has been proposed to correspond to approximately 50 incident infectious cases per 100 000 population [8]. This correlation between TB incidence and ARTI has been questioned since this was established in the pre-chemotherapy era. The duration of infectiousness, coupled with the incidence of new infectious cases, is reflected in the prevalence of such cases (i.e., prevalence is a function of incidence and duration). As soon as an effective intervention is introduced, the duration of infectiousness is reduced, transmission is decreased and the relation between prevalence and incidence is disturbed [10,11]. This was shown for the United States before HIV had a noticeable impact on tuberculosis. Here, extrapolation required over 400 incident cases per 100 000 population to result in a 1 per cent risk of infection [12].

It could thus be that the true incidence of TB in Vietnam is higher and thereby the case detection rate of the NTP is lower than has been estimated by WHO [6,7]. Besides the problem with interpretation of results of tuberculin survey and estimation of TB incidence from ARTI, the single countrywide estimate of TB incidence does not take into account the substantial geographic variation in TB epidemiology across the country (Chapter 5), notably a north-south gradient in ARTI and notification rates (Chapters 2,5,6).

Lower CDRs than estimated by the WHO have been suggested by two local surveys of TB prevalence. A population based study done in 2000 in Bavi, a rural district in the northern part of the country, found a prevalence of smear-positive TB of 60/100 000 among men and 79/100 000 among women [13]. The estimated CDR in Bavi district (45%) was far from the reported national CDR (80% in 2000) [6]. Recently a TB prevalence survey in Hanoi (2003-2004), the capital in the north of the country, showed that the sputum smear-positive prevalence rate was 146/100 000 in persons aged 15 years old or more while the notification rate was reported to be much lower (40/100 000 in 2004) [14]. From these data, the CDR can be estimated as 35% [15].

Although 100% of districts had DOTS services by 1997 (Chapter 2), there has been further expansion of DOTS services within districts since then. The grass-root laboratory network for AFB smear microscopy has been well established and is easily accessible to the population (Chapter 4) [1]. The proportions of the population examined vary by region reflecting both the size of the TB problem and the utilization of health services (Chapter 5). For the period of 2001-2005, the proportions of the population who had a sputum smear examined ranged from 0.74% in 2001 to 0.79% in 2005 and the positive rates were around 10.5% [2]. This expansion of DOTS services resulted in an overall increased case detection. A smear-positive rate of around 10% is often regarded to reflect adequate case finding in practice. However, the proportion of the population of Vietnam that was examined by direct microscopy on suspicion of TB (0.74% in 2001) was much lower compared with that in Peru (approximately 5% every year, by 1999) [16] where an impact of the DOTS programme on TB incidence was observed. Thus, the proportion of the population examined in Vietnam could, in fact, represent a CDR that is below 70%.

The findings in chapters 3 and 4 suggest gender-related barriers to access to NTP services. More men than women were examined by microscopy, but also the proportion of men with positive smears was higher than the proportion of women (Chapter 3). The sex difference in smear positive rate, as well as in notification rate, suggests either biological differences, e.g. men may have higher TB incidence than women or higher the bacillary load of sputum specimens, or lower access to TB diagnosis for women [17-19]. However, in Hanoi (2003-2004), by active case finding, the male:female ratio of TB patients detected was 0.7 [14]. In addition, we found longer delay for women (chapter 3). These data, and data from other studies [13,20-23], suggest that reported incidence/notification rates for TB may under-represent women.

Chapter 3 and 5 indicated that distance to the district health center was a key factor determining access to TB services, suggesting under-diagnosis in areas further away from health facilities. In addition, our findings showed that CNR and suspect rate varied by zones and urbanity setting (Chapter 5). Thus under-diagnosis may happen in certain zones as well as in urban or rural settings. However, poverty status or ethnic composition apparently plays no major role in differences in CDR (Chapter 5).

In some settings, an important source of unnotified tuberculosis cases is the private sector. Despite the presence of an effective low-cost or free NTP, a significant number of TB patients may opt for diagnosis and treatment by private practitioners [24-26]. Part of the reason for failing to bring about a more rapid reduction in tuberculosis incidence worldwide is the lack of effective involvement of all practitioners-public and private-in the provision of high quality tuberculosis care [27]. What proportion of sputum smear-positive cases of tuberculosis are managed in the private sector remains unclear. In India between 60 and 88% of suspect tuberculosis cases first approached the private sector for their diagnosis and treatment [28-30].

In Vietnam, no data are available on overall magnitude of private health sector involvement in TB care. Studies on the private sector in HCMC showed that about 50% of all TB patients in the NTP have been in contact with the private sector prior to attending the NTP, and that about 40% of all prevalent TB cases received treatment with anti-TB drugs in the private sector [31-33]. In our study on diagnostic delay (chapter 3), we found that 36% of patients had first consulted the facilities out-side the NTP. The NTP case detection in HCMC increased by 18% as a result of referral of TB suspects from private providers to NTP services [34-35]. These data suggest that there is a large contribution of the private sector in diagnosis and treatment of new smear-positive TB cases which leads to an underestimate of TB incidence by the TB case notification because the private sector does not report.

**Accuracy of reported cure rates**

Effective diagnosis and treatment of tuberculosis can rapidly reduce the risk of infection [36]. With short course chemotherapy, the overall cure rate of new smear positive TB

patients who were treated in NTP facilities was more than 90% (Chapter 1), surpassing the WHO target of 85%. However, cure rates of smear-positive patients may be overestimated due to the following problems.

Cure is defined as a negative sputum smear at months 5 and 8 of treatment. Because at both occasions only a single smear is examined, false-negative reading of these follow-up smears is possible [37]. Moreover, the laboratory quality control system used in Vietnam has limited power for detecting false-negative follow-up smears [38], and the incentive system may affect reporting of failure cases. However, we showed that, at least in the north of the country, the relapse rate (9.9%) was not in excess of that expected with the regimen used, suggesting that few treatment failures are missed (Chapter 7).

The non-increasing levels of drug resistance, in particular the stable level of MDR, among new smear-positive patients (Chapter 7) suggest that treatment does not result in increasing transmission of MDR-TB in the southern part of the country, and are thus compatible with high cure rates and low failure rates of new smear-positive patients. The high prevalence of MDR among retreatment patients is in accordance with the high failure rates among patients who failed on retreatment.

A limitation of these findings may be that the drug resistance surveys conducted in the south of Vietnam (Chapter 7) included only patients presenting to NTP facility but not those diagnosed in the private sector. Prevalence of multidrug resistance in these patients may be higher since overall treatment outcome was very poor in the private sector [31-33], while high cure rate were only confirmed within the NTP. Private sector treatment may thereby create chronic cases and contribute to sustained transmission of (drug resistant) TB. We nonetheless believe that exclusion from our surveys of patients treated in private sector has not affected our prevalence estimates of MDR among new patients. It would only do so if patients who failed or relapsed after treatment in the private sector preferentially transmitted to people who, when having TB, also turn to the private sector for treatment, and it shows unlikely that such aggregation of transmission occurs at a relevant scale.

**Progression rates of infection to disease**

TB incidence may not decline despite high case detection and cure rates if the risk of progression from TB infection to TB disease is higher than assumed by the model. The most important cause of such increased progression rates would be HIV infection, but other factors may also play a role.

In Vietnam, the prevalence of HIV is still low. The epidemic is in the concentrated stage and mainly occurring among young adults (20-39 years old). The HIV-epidemic is predominant among males and this has not changed in the last 10 years [39]. The age-sex groups with highest HIV prevalence were the same as those in which the rise in tuberculosis CNR is most pronounced in our findings (Chapter 6). In our study, we found the steepest increase in CNR among young adults (Chapter 6). Data from HCM City showed that the HIV prevalence among TB patients increased from 1.5% in 1997-1998 to

9.0% in 2001-2002 [40] and the direct impact of HIV on TB notification of new smear-positive attributed to HIV was 1.9% per year, being more pronounced among men aged 15-34 years old [41]. Although we did not collect HIV data, the emerging HIV epidemic may thus be an important explanation for the observed increase in CNR among young adults. However, HIV prevalence in the general population above 40 years old is still low. Thus, direct impact of HIV does not explain why the decline in CNR among the older age groups is less than predicted by the WHO model (Chapter 6).

Diabetes mellitus compromises the immune system and predisposes to development of TB disease in infected persons. Studies showed that diabetes mellitus and tuberculosis were strongly associated [11,42-45]. During the last decade, the social-economic situation in Vietnam has undergone rapid changes, strongly affecting the lifestyle and dietary habits of the people. Over 10-year period, the prevalence of diabetes in Vietnamese adults increased substantially from 1.2% (1.6% prediabetes) in 1990 to 2.7% (7.3% prediabetes) in 2002. Most of people with diabetes had type 2 (maturity onset) diabetes [46-48]. This prevalence was 3.8% (2001) in HCMC [49]. The increase in diabetes could thereby explain a small part of the shortfall in decline in CNRs of tuberculosis in the middle aged and elderly population.

Globally, malnutrition, active smoking and indoor air pollution may be risk factors for TB that are only second to HIV infection and diabetes [11,50]. Tobacco smoking may increase risks of both TB infection and progression to TB disease. Vietnam has the highest reported male smoking prevalence rate in the world. Smoking prevalence was 72% among adult men and 4% among adult women [51]. Different smoking habits could thereby explain part of the sex difference in decline in CNRs. However, there is little or no data on the extent of that contribution.

Genetic analyses of circulating *M. tuberculosis* strains have shown that the Beijing genotype is highly prevalent in East and Southeast Asia, and some studies have suggested that this genotype is spreading with or without an association with drug resistance [52,53].

Two studies that analyzed *M. tuberculosis* strains isolated in Vietnam showed that 55% belonged to the Beijing genotype family. The Beijing genotype was associated with young age [54], suggesting recent spread, and was found more frequently in patients with treatment failure or relapse [55]. Spread of the Beijing genotype could contribute to sustained or increased transmission by increasing failure and relapse rates, and thereby to non-decline or even increase of CNRs. However, the patients in these studies were not from a representative sample and the association of Beijing genotype with young age may reflect confounding by e.g. hospitalization. Any effect on failure or relapse is apparently limited given the low failure rates and, at least in the north of the country, a relapse rate that is not in excess of that expected with the 8-month regimen (chapter 7).

**Transmission rates**

Finally, a decline in TB incidence may not be observed if transmission between infectious patients and uninfected people occurs more than expected (i.e. infectious cases result in more secondary infections than assumed in the models). Such increased transmission rates in Vietnam may exist for a number of reasons.

TB treatment not only prevents infectious patients from dying, but cures them and prevents them from becoming chronic cases, i.e. patients who have not been cured by the standard first-line drug regimens used in the NTP. The NTP had a high cure rate (more than 90%) and a low failure rate (1%) of the so-called category 1 treatment of new smear-positive TB patients. However, the failure rate of smear-positive retreatment patients who had first failed this treatment category I was rather high (17.5%). As a consequence, about 350 chronic cases have been developing each year, for which, in the absence of second-line (MDR) treatment, the NTP has no treatment to offer [2]. This does not include patients treated in private sector. A study in Ho Chi Minh City showed that 90% of chronic cases had MDR-TB [56]. In view of the long duration of illness, the prevalence of MDR-TB cases will increase due to their accumulation over time, which may result in increasing contribution to sustained transmission of (drug resistant) TB. To what extent this increasing prevalence of chronic TB explains the shortfall in declining TB incidence is unknown. The non-increasing MDR prevalence in the south of Vietnam (Chapter 8) suggests that this is limited but the observation period may be too short to see an impact on MDR prevalence among new patients.

The increase in incidence of TB due to HIV infection may lead to more transmission. However, data from Tanzania [57] suggested this does not need to happen in a setting of moderate HIV prevalence and a well-functioning DOTS program. This may be different in Vietnam with a concentrated HIV epidemic. This may be the case among adolescents and young adults who tend to aggregate in e.g. workplaces and schools.

Between 1994 and 1999, nearly 4.5 million people (6.5% of the population over 5 years of age) changed their residence. The 1999 census data indicated that migration to urban areas accounted for over 53% of all moves, mainly to Hanoi and HCMC. 1.2 million people moved from rural settlements to urban areas [58]. HCMC is a center of migration activities, being the largest recipient of inter-provincial migration. The city's net migration rate of 8.2% is highest in the country. Every year the city receives around 700,000 migrants from other region. The figure for Hanoi was 4.3% In Vietnam, internal migrants are predominantly young adults. Over half of internal migrants (52%) were less than 25 years old [58,59]. Recent immigrants in urban areas are generally poor. Crowding and bad housing conditions may increase contact rates and thereby increase (or reduce decline of) TB transmission However, data on the role of urbanization and migration are limited.

## IMPLICATION FOR TUBERCULOSIS CONTROL

This study addresses the impact of DOTS Strategy on the TB epidemic at the level of national TB control programme. The observations from this thesis have a number of implications for TB control programme in Vietnam and elsewhere.

First, the DOTS Strategy is feasible in a low-income, high-burden country (Chapter 2) but the effects of DOTS on the incidence of TB appear limited in the Vietnam setting (chapter 6). This apparent failure of DOTS as a TB control strategy does not mean this approach had no benefit. The DOTS programmes improved case detection, treatment outcome (chapter 2) and prevented the emergence of drug resistance (Chapter 8) and thus should be implemented further. However, in response to the lack of impact, further efforts are needed to ensure provision of high quality DOTS services at all levels of health service delivery and to rapidly move beyond from the basic DOTS Strategy to the expanded DOTS Strategy (Stop TB Strategy) [60,61] with more focus on the new challenges in TB control in Vietnam.

Second, TB incidence is increasing in young adults (Chapter 6) in association with spreading of the HIV epidemic calling for a commitment to prevent both TB and HIV. This will require close cooperation and collaboration between HIV and TB programmes to implement the WHO's "Interim Policy on Collaborative TB/HIV Activities" [62]. This interim policy provides guidelines that define specific activities to address this dual epidemic. Control of the future HIV driven TB epidemic in Vietnam cannot move forward without coordinated leadership of the Government through the National HIV/AIDS Program and NTP to develop a balanced TB/HIV policy and health sector response. The Stop TB Strategy to control HIV-related TB will be successful only through patient-centred, countrywide TB and HIV collaborative service delivery, complemented by a major initiative to strengthen the health system

Third, though levels of (multi)drug resistance among new smear-positive patients have not increased over the past six years in the absence of second-line treatment (chapter 8), it is nevertheless recommended to introduce 'programmatic management of MDR-TB' [60,61,63] for the following reasons:

- Treatment of MDR-TB patients with second-line drugs is feasible even in poor setting [64,65] and saves lives of patients with high mortality who deserve to be cured
- Unmeasured extent of MDR-TB in a growing private sector
- MDR-TB cases will accumulate over time increasingly spreading MDR TB into the community
- To prevent spread of MDR-TB in populations with a high prevalence of HIV, such as in prisons and rehabilitation centres.

This involves diagnosing MDR-TB through quality-assured culture and drug susceptibility testing, and treating patients with second-line drugs under proper case-management

conditions [63]. Second-line TB treatment must be mainstreamed into a countrywide TB control plan.

Fourth, our findings indicate that initial visit to the private sector had a considerable impact on the length of delays in TB patients diagnosed in the NTP (Chapter 3). It is critical to develop public-private mix approaches as a means to expand and strengthen DOTS, with an emphasis on establishing a referral system and improving case detection and treatment success [66]. In addition, it is important to ensure all care providers are involved and deliver to all patients the DOTS international standard of care and support [27].

Fifth, the efficiency of sputum smear examination can be improved. The incremental return on specimens subsequent to the second sputum specimen was small (chapter 3). Omitting the third sample has limited impact on the diagnostic sensitivity while it saves a lot of work and burden to the patient (Chapter 3). The examination of 2 consecutive sputum smears is almost as efficient as culture for detecting cases [67]. These results led to a recommendation of only two consecutive sputum specimens for tuberculosis diagnosis that should be considered by the NTP.

Sixth, though this thesis was inconclusive about gender differences in TB access and case notification (Chapters 3, 4). However, several studies in Vietnam showed gender-related differences in health seeking and barriers to access [20-23]. More information on gender-related barriers to access to NTP services at the local and national levels should be collected and analyzed. Prevention and control strategies should be adapted accordingly. New community–based and public-private service approaches that aim to increase access and effective treatment, especially for those most vulnerable, should seek to address known gender-related barriers to care.

Seventh, the distance to the district health center was a key factor determining access to TB services (Chapter 5), suggesting under-diagnosis in areas further away from health facilities. Measures should be explored to provide adequate laboratory services for those areas by transporting either specimens or fixed smear slides prepared by a local health worker after training to district laboratories or establishment of more than 1 microscopy centers in districts with a large population or a large area, in order to bring the TB diagnostic service close to the community. However, the number of microscopy centres, the quality of performance and the cost-effectiveness of the extra microscopy centers in the district should be considered by each provincial TB center.

Finally, the variation in TB epidemiology according to zones and urban-rural settings (Chapter 5) required further analysis to develop specific TB control strategies for each geographical area and setting with the appropriate investment. Though in this study, both case notification and suspect rates clearly showed no relevant association with ethnic composition and poverty status, poverty status and ethnicity at level of individual patients should be further explored.

## RECOMMENDATIONS FOR FURTHER RESEARCH

In order to have base-line data as well as to assess trend of TB burden and TB control effect over time in the country, periodical nationwide TB prevalence and tuberculin surveys should be conducted. The trends of TB drug resistance including MDR and XDR in the country need to be monitored routinely.

Operational research is required to identify potential flaws in case detection and treatment in order to improve them, and to investigate the causes of increase in TB incidence among young adult patients. Important issues to explore would be the direct and indirect impacts of HIV on TB epidemic to improve the care of people who are infected with both TB and HIV, gender-related issues and links between TB and poverty at individual level for equal access to TB care. In addition, studies are needed to estimate the extent of private sector involvement, and of the impact of private-public mix DOTS on case detection and treatment, as well as to identify key issues for private-public mix DOTS in order to develop new approaches to involve the private sector in DOTS implementation.

Other potential determinants and risk factors such as diabetes, smoking, malnutrition, indoor air pollution, urbanization, immigration, and genotype are needed to be investigated as well.

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# Summary

This thesis includes studies addressing the impact of DOTS Strategy on the TB epidemic in Vietnam – a high tuberculosis burden country that has reported case detection rates and cure rates well above the global targets for TB control over 10 years - at the level of national programme.

In chapter 1, an overview of the global TB burden, the natural history of tuberculosis, methods for measuring the impact of TB control is provided as well as information on TB and its TB control in Vietnam. The rationales and general objectives of the study are given.

The World Health Organization, the Global Stop TB Partnership, and the Millenium Development Goals have all adopted the following 2005 targets for tuberculosis control: to detect at least 70% of all estimated sputum smear-positive cases and to treat successfully at least 85% of them. Achievement of these targets for case detection and cure is expected to reduce the annual TB incidence rate by 8-12% per year and an even faster reduction in mortality of 9–13% per year, in the absence of HIV co-infection. At 7% annual decline, incidence would be halved in 10 year. These theoretical figures are supported by evidence from Europe and developing countries. The DOTS Strategy (the WHO-recommended approach to tuberculosis control based on 5 essential elements) is considered the key to successful TB control. However, more than a decade after implementing DOTS Strategy, TB cases continue to rise worldwide. The HIV pandemic and MDR-TB constitute massive challenges to global TB control in particular in sub-Saharan Africa and Eastern Europe.

Among the 22 countries with the highest burden of TB cases, Vietnam is thus far the only one that has consistently reported case detection rates and cure rates above the WHO targets over the last years [WHO report 2007]. However, TB case notification rates in Vietnam as reported to WHO show no decline. This makes Vietnam an important setting for closely studying the impact of the DOTS Strategy on the TB epidemic.

The question is whether a DOTS programme that reaches the WHO's targets sufficient to control the TB epidemic. This has been addressed in Vietnam by evaluating the quality and completeness of case detection by the Vietnamese national tuberculosis control programme (diagnostic delay among newly diagnosed smear-positive TB patients, use and yield of sputum smear microscopy by age and sex, geographic patterns of the proportion of the population examined and the proportion of smear-positives) and by assessing the impact of control on the TB epidemic (trends in case notification and annual risk of TB infection (ARTI), extent of relapse among patients successfully treated for new smear-positive pulmonary tuberculosis and prevalence of drug resistance among TB patients and its trend over time).

Chapter 2 is a descriptive study based on routine NTP surveillance data on the establishment and development of the National Tuberculosis Control Programme of Vietnam for the period 1986-2000.

Among 22 highest TB burden countries in the world, the NTP of Vietnam introduced the DOTS Strategy in 1989 and achieved 100% DOTS coverage in 2000. The proportion of smear-positive cases detected and put on short-course treatment was over 70% since 1996. Reported cure rates with short-course chemotherapy were consistently over 85%. This showed that DOTS is feasible in a low-income, high-burden country. However, TB case notification rates in Vietnam show no decline.

In chapter 3, diagnostic delay was assessed through a cross-sectional survey of all consecutively registered new smear positive pulmonary TB patients during one quarter who were treated by the National Tuberculosis Control Programme by interviewing using a pre-coded structured questionnaire.

On average, total, patient and health care provider delays in TB diagnosis and treatment nation-wide were short in Vietnam. Median (range) delay was 4 weeks (1-48) for total, 3 (1-48) weeks for patient and 1 (0-25) week for health care delay. Nonetheless, 15% of patients reported total delay ≥12 weeks, and accounted for 49% of the cumulative number of delay-weeks. Initial visit to the private sector had a considerable impact on the length of delays but with distinct regional differences across the country.

Chapter 4 assesses the use and yield of sputum smear examination by the NTP, and its variation by age and sex with emphasis on gender differences in access to care, in a representative survey in the northern part of Vietnam. A cross-sectional study was conducted by retrospective reviews of tuberculosis laboratory registers of 30 randomly selected laboratories.

In the north of Vietnam, 9.7 suspects were examined and 29.3 smears done to find one smear-positive case. The smear-positive rate was 10.3%. The male:female ratios were 1.36 among TB suspects and 1.89 among smear-positive patients, suggesting higher TB incidence among men rather than lower access to TB facilities for women. The third smear examination could be omitted.

In chapter 5, the variation of TB suspect and notification rates were evaluated by retrospective reviews of all district TB laboratory registers by individual commune for one quarter by in a cross-sectional survey.

The overall annual notification rate of smear positive TB per 100 000 population was 78; 9 per 1000 population had sputum smear examination. The case notification rates (CNR) were higher in the south and centre than in the north of the country. Geographical variations in CNRs largely reflected true epidemiological differences in TB distribution in Vietnam. CNRs varied remarkably by latitude, zone and urbanity and were not associated with poverty or ethnicity at commune level. The distance to the district health center was a key factor determining access to TB services, suggesting under-diagnosis in areas further away from health facilities.

In chapter 6, the trends in annual risk of tuberculosis infection were estimated from repeated tuberculin surveys and compared with trends in case notification rates in six sentinel provinces where the DOTS Strategy had been introduced in the 1980s.

The age-standardised notification rates in the period 1996-2003 declined significantly by 2.6 to 5.9% per year in five provinces. However, notification rates in the age group 15-24 years increased significantly by 4.5 to 13.6% per year during this period in four. The mean age of newly diagnosed patients with smear-positive tuberculosis increased up to 1995 but decreased afterwards. The annual risk of tuberculosis infection showed significant annual decrease (4.9% per year) in one province in surveys done between 1986 and 1997, in two (6.6 and 14.7%) and no decline in other 3 provinces in surveys done between 1993 and 2002.

Chapter 7 assesses survival and bacteriologically confirmed relapse rate after 12-24 months among new smear-positive pulmonary TB patients who completed treatment. Data were colleted from a cohort of patients treated in 32 randomly selected districts in the northern part of Vietnam

Among 304 patients included in the study, the bacteriology relapse rate was 5%. An additional 4% started TB retreatment. Four of 12 culture-positive relapse cases (33%) had multidrug-resistant strains. In total, the relapse proportion was 9.9%. The relapse rate was not in excess of that expected from a randomized controlled trial with the 8-month regimen.

Chapter 8 presents the results of a drug resistance survey. This survey was conducted by collecting sputum specimens from consecutively diagnosed patients with smear-positive TB at 40 randomly selected public TB clinics in the south of Vietnam. *M. tuberculosis* isolates were tested for susceptibility to first-line drugs.

Among new patients, the prevalence of resistance to any drug was 26% and the prevalence of MDR 1.8%. Among previously treated patients, prevalence of any resistance and MDR was 63% and 23% respectively. The prevalence of resistance to any drug has significantly declined and levels of (multi)drug resistance among new smear-positive patients have not increased over the past six years in the absence of second-line treatment. Therefore, a DOTS program can contain drug resistant TB in this setting.

In **chapter 9**, the main findings and major limitations are discussed as well as the implications of these studies for TB control programme and recommendations for further research.

In conclusion, TB control in Vietnam failed to have the expected impact. Initial indirect assessments of case detection and cure rates did not identify major problems. Better, more direct evaluation of case detection and treatment outcome are indicated. The increase among adolescents recognized a specific explanation.

# Tóm tắt

Bản luận văn này bao gồm những nghiên cứu về tác động của chiến lược DOTS tới tình hình bệnh lao tại Việt nam – quốc gia có tình hình dịch tễ bệnh lao cao đã đạt được tỷ lệ phát hiện và tỷ lệ khỏi cao hơn mục tiêu phòng chống lao toàn cầu từ hơn 10 năm qua.

Chương 1 trình bày tổng quan dịch tễ bệnh lao toàn cầu, xu hướng phát triển tự nhiên của bệnh lao, các phương pháp đánh giá tác động của công tác phòng chống lao lên tình hình dịch bệnh, cũng như các thông tin cơ bản về Việt nam và công tác phòng chống lao tại Việt nam. Cơ sở khoa học và mục tiêu nghiên cứu cũng được đưa ra trong chương này.

Tổ chức Y tế thế giới (TCYTTG), Tổ chức Đối tác Ngăn chặn bệnh lao toàn cầu (Stop TB Partnership) đã thông qua mục tiêu phòng chống lao đến năm 2005 là phát hiện tối thiểu 70% số bệnh nhân lao phổi mới và điều trị khỏi tối thiểu 85% cho số bệnh nhân đó. Khi đạt được mục tiêu về phát hiện và điều trị khỏi, ước tính tỷ lệ bệnh lao mới hàng năm sẽ giảm từ 8-12% mỗi năm và tỷ lệ tử vong thậm chí sẽ giảm nhanh hơn từ 9-13% mỗi năm trong bối cảnh không có đồng nhiễm HIV. Và như vậy, với 7% giảm bệnh lao hàng năm, tỷ lệ bệnh lao mới sẽ giảm còn một nửa trong vòng 10 năm tới. Các con số lý thuyết này đã được minh chứng tại châu Âu và các nước đang phát triển. Chiến lược DOTS (do TCYTTG khuyến cáo dựa trên 5 thành tố thiết yếu) được xem là điểm then chốt để phòng chống bệnh lao một cách hiệu quả. Tuy nhiên, trên một thập kỷ kể từ sau khi bắt đầu triển khai chiến lược DOTS, số bệnh nhân lao vẫn tiếp tục gia tăng trên phạm vi toàn cầu. Đại dịch HIV phối hợp với bệnh lao kháng đa thuốc là thách thức lớn cho công tác phòng chống lao toàn cầu, đặc biệt tại khu vực Cận Sahara châu Phi và Đông Âu.

Trong 22 quốc gia có tình hình dịch tễ bệnh lao cao, Việt nam là quốc gia duy nhất đạt tỷ lệ phát hiện và kết quả điều trị khỏi cao hơn các mục tiêu của TCYTTG trong nhiều năm [Báo cáo của TCYTTG năm 2007] . Tuy nhiên, tỷ lệ thu dung bệnh lao tại Việt nam theo báo cáo cho TCYTTG là chưa thuyên giảm. Chính điều này làm cho Việt nam trở thành địa bàn lý tưởng để nghiên cứu sâu về tác động của chiến lược DOTS lên tình hình dịch bệnh lao.

Vấn đề đặt ra là khi một chương trình chống lao áp dụng Chiến lược DOTS đạt được mục tiêu của TCYTTG về phòng chống bệnh lao có đủ điều kiện để khống chế dịch bệnh lao. Vấn đề này được nghiên cứu tại Việt nam bằng cách đánh giá chất lượng, độ tin cậy và tính đầy đủ của biện pháp phát hiện chẩn đoán trong Chương trình Chống lao quốc gia (CTCLQG) (thời gian chẩn đoán chậm trễ bệnh nhân lao phổi AFB(+) mới, sử dụng và hiệu quả của xét nghiệm soi đờm trực tiếp theo giới và tuổi, tỷ lệ dân số được xét nghiệm đờm soi trực tiếp và tỷ lệ xét nghiệm dương tính theo khu vực địa lý) và bằng cách đánh giá tác động của công tác phòng chống lao lên tình hình dịch bệnh lao (xu hướng thu dung và nguy cơ nhiễm lao hàng năm, tình hình tái phát sau điều trị của bệnh nhân lao phổi AFB(+) mới đã hoàn thành điều trị và tỷ lệ kháng thuốc trong bệnh nhân cũng như xu hướng kháng thuốc theo thời gian).

Chương 2 trình bày nghiên cứu dịch tễ học mô tả dựa trên số liệu của hệ thống giám sát thường kỳ của CTCLQG về sự hình thành và phát triển của CTCLQG trong giai đoạn 1986-2000.

CTCLQG Việt nam đã triển khai chiến lược DOTS từ năm 1989 và đạt độ bao phủ 100% dân số trong cả nước vào năm 2000. Tỷ lệ bệnh nhân AFB(+) mới thu dung vào hoá trị liệu ngắn ngày (HTLNN) chiếm trên 70% số bệnh nhân ước tính từ 1996. Tỷ lệ điều trị khỏi với HTLNN đạt trên 85%. Điều này cho thấy chiến lược DOTS là khả thi tại một quốc gia có thu nhập thấp và có tình hình dịch bệnh lao cao. Tuy nhiên, tỷ lệ thu dung bệnh nhân lao vẫn chưa thuyên giảm tại Việt nam.

Trong chương 3, thời gian chậm trễ trong chẩn đoán được đánh giá qua điều tra cắt ngang toàn bộ bệnh nhân lao phổi AFB(+) mới được đăng ký điều trị trong 1 quý trong CTCLQG bằng cách phỏng vấn qua phiếu phỏng vấn được thiết kế trước.

Ở Việt nam, tổng thời gian chậm trễ, chậm trễ do người bệnh và chậm trễ do thầy thuốc trong chẩn đoán và điều trị bệnh nhân lao là ngắn. 4 tuần (khoảng 1-48 tuần) là trung vị đối với tổng thời gian chậm trễ, 3 (1-48) tuần đối với thời gian chậm trễ do người bệnh và 1 (0-25) tuần là thời gian chậm trễ do thầy thuốc. Tuy nhiên, 15% số bệnh nhân có tổng thời gian chậm trễ trên 12 tuần và chiếm tới 49% tổng số thời gian chậm trễ cộng dồn. Việc tiếp cận với y tế tư trong lần khám đầu tiên có tác động đến thời gian chậm trễ nhưng có sự khác biệt giữa các vùng trong toàn quốc.

Chương 4 đánh giá việc sử dụng và kết quả xét nghiệm đờm soi trực tiếp trong CTCLQG, và sự thay đổi của kết quả này theo tuổi, giới với nhấn mạnh về sự khác biệt về giới trong tiếp cận và chăm sóc y tế đại diện cho khu vực miền Bắc Việt nam. Nghiên cứu cắt ngang đã được tiến hành bằng cách hồi cứu lại các sổ xét nghiệm của 30 huyện được lựa chọn ngẫu nhiên.

Tại miền Bắc, để phát hiện được 1 bệnh nhân lao phổi AFB(+) cần khám và cho xét nghiệm đờm 9.7 người nghi lao và làm xét nghiệm 29.3 tiêu bản đờm. Tỷ suất nam:nữ là 1.36 trong số người nghi lao đến khám và 1.89 trong số bệnh nhân dương tính, điều này cho thấy tỷ lệ mắc lao trong nam giới cao hơn chứ không phải do sự tiếp cận với cơ sở khám chữa lao thấp hơn ở nữ giới. Nghiên cứu cũng đưa ra khuyến cáo không nên xét nghiệm mẫu đờm thứ 3.

Trong chương 5, sự thay đổi của tỷ lệ người nghi lao được xét nghiệm đờm và tỷ lệ thu dung bệnh lao theo từng xã trong 1 quý được đánh giá qua hồi cứu sổ xét nghiệm của toàn bộ các huyện trong cả nước thông qua nghiên cứu cắt ngang.

Tỷ lệ thu dung bệnh nhân lao phổi AFB(+) hàng năm là 78/100.000 dân và 9/1000 người dân được xét nghiệm đờm soi trực tiếp để tìm vi khuẩn lao. Tỷ lệ thu dung tại các xã thuộc khu vực miền Trung và miền Nam cao hơn so với các xã thuộc khu vực miền Bắc. Sự thay đổi của tỷ lệ thu dung mang tính chất địa lý phản ánh sự khác nhau thực sự về tình hình dịch tễ trong phân bố dịch tễ bệnh lao tại Việt nam. Tỷ lệ thu dung khác nhau rõ rệt theo vĩ độ, khu vực và tình trạng thành thị nông thôn và tỷ lệ thu dung không liên quan đến tình trạng nghèo đói và dân tộc thiểu số tại cấp xã. Khoảng cách từ trạm y tế xã đến trung tâm y tế

huyện là yếu tố quan trọng để đánh giá tình hình tiếp cận với dịch vụ khám chữa bệnh lao, điều này cho thấy các khu vực nằm cách xa các cơ sở y tế cho tỷ lệ chẩn đoán thấp.

Trong chương 6, xu hướng nguy cơ nhiễm lao được ước tính thông qua các điều tra nguy cơ nhiễm lao lặp lại và so sánh với tỷ lệ thu dung tại 6 tỉnh giám sát trọng điểm đã triển khai chiến lược DOTS từ những năm 1980.

Tỷ lệ thu dung hiệu chỉnh theo tuổi trong giai đoạn 1996-2003 giảm có y nghĩa từ 2.6%-5.9% mỗi năm tại 5 tỉnh. Tuy nhiên, trong giai đoạn này, tỷ lệ thu dung trong nhóm 15-24 tuổi tăng có ý nghĩa từ 4.5% lên 13.6% mỗi năm tại 4 tỉnh. Tuổi trung bình của bệnh nhân lao phổi AFB(+) mới tăng trong giai đoạn trước năm 1995 và giảm sau đó. Nguy cơ nhiễm lao hàng năm giảm (4.9% mỗi năm) tại 1 tỉnh trong giai đoạn 1986-1997 và tại 2 tỉnh (6.6% và 14.7% mỗi năm) và không giảm tại 3 tỉnh khác trong giai đoạn 1993-2002.

Chương 7 xác định tỷ lệ tái phát bằng xét nghiệm vi trùng học sau 12-24 tháng của lô bệnh nhân lao phổi AFB(+) mới đã hoàn thành điều trị. Số liệu được thu thập thông qua nghiên cứu thuần tập những bệnh nhân đã hoàn thành điều trị tại 32 huyện chọn ngẫu nhiên tại các tỉnh khu vực miền Bắc.

Với 304 bệnh nhân tham gia nghiên cứu, tỷ lệ tái phát dựa theo xét nghiệm vi trùng học là 5%. Bổ sung 4% đã điều trị tái trị bệnh lao. 4/12 (33%) bệnh nhận tái phát dựa theo kết quả nuôi cấy và kháng sinh đồ là chủng vi khuẩn kháng đa thuốc. Tổng cộng, tỷ lệ tái phát là 9.9%. Như vậy, tỷ lệ tái phát không cao hơn so với kết quả tái phát theo nghiên cứu thử nghiệm lâm sàng công thức 8 tháng.

Chương 8 trình bày kết quả điều tra kháng thuốc. Điều tra này đươc tiến hành bằng cách thu thập mẫu đờm của bệnh nhân lao phổi AFB(+) được chẩn đoán liên tục tại 40 quận/huyện được chọn ngẫu nhiên tại khu vực miền Nam. Vi trùng lao phân lập được xét nghiệm kháng sinh đồ với các thuốc chống lao hàng I.

Đối với bệnh nhân lao mới, tỷ lệ kháng thuốc lao là 26% và tỷ lệ kháng đa thuốc là 1.8%. Đối với bệnh nhân đã điều trị thuốc lao, tỷ lệ kháng thuốc và kháng đa thuốc tương ứng là 63% và 23%. Tỷ lệ kháng thuốc lao giảm có ý nghĩa thống kê và tỷ lệ kháng đa thuốc không tăng trong vòng 6 năm trong bối cảnh CTCLQG chưa áp dụng quản lý điều trị bệnh lao kháng thuốc bằng thuốc chống lao hàng 2. Do vậy, Chiến lược DOTS có khả năng ngăn cản kháng thuốc trong bối cảnh này.

Trong chương 9, các kết quả và các hạn chế chính của nghiên cứu được thảo luận cũng như các khuyến cáo rút ra từ nghiên cứu này cho CTCL và các nghiên cứu cần triển khai trong tương lai.

Tóm lại, công tác phòng chống bệnh lao tại Việt nam có tác động rất hạn chế trong việc làm giảm tình hình mắc lao như mong muốn. Các đánh giá gián tiếp về phát hiện và điều trị không xác định được vấn đề gì lớn. Các đánh giá trực tiếp bổ sung về phát hiện và kết quả điều trị đã được chỉ ra. Bệnh lao gia tăng ở nhóm người trẻ tuổi được coi là một sự giải thích rõ ràng cho tác động hạn chế này.

# Samenvatting

Dit proefschrift beschrijft onderzoeken naar het effect van de DOTS strategie op de tuberculose epidemie in Vietnam. Vietnam is een land met een hoge tuberculose-ziektelast. De laatste 10 jaar overtreffen, op het niveau van het nationale tuberculose bestrijdingsprogramma (NTP), de gerapporteerde tuberculose-opsporingspercentages en genezingspercentages de wereldwijde doelstellingen voor tuberculosebestrijding.

In hoofdstuk 1 wordt een overzicht gegeven van de wereldwijde tuberculose-ziektelast, van het natuurlijk beloop van tuberculose, en van methoden voor het meten van het effect van tuberculosebestrijding. Ook wordt informatie over tuberculose en de tuberculosebestrijding in Vietnam samengevat, en worden de rationale en de algemene doelstellingen van het onderzoek gegeven.

De Wereldgezondheidsorganisatie (WHO), de Global Stop TB Partnership en de Millenium Development Goals hebben voor het jaar 2005 de volgende doelen voor tuberculosebestrijding gesteld: opsporing van ten minste 70% van alle geschatte sputum-positieve gevallen, en succesvolle behandeling van ten minste 85% van deze gevallen. Indien deze doelstellingen voor gevalsopsporing en genezing worden bereikt, wordt een daling van de tuberculose-incidentie verwacht met 8-12% per jaar, evenals een zelfs snellere daling van de sterfte aan tuberculose met 9-13% per jaar, dit in de afwezigheid van HIV co-infectie. Bij een daling van 7% per jaar zou dan de incidentie van tuberculose in 10 jaar tijd worden gehalveerd. Deze theoretische getallen worden ondersteund door gegevens uit Europa en ontwikkelingslanden. De DOTS strategie (de door de WHO aanbevolen aanpak van tuberculosebestrijding, gebaseerd op 5 essentiële elementen) wordt beschouwd als de sleutel voor succesvolle tuberculosebestrijding. Echter, meer dan 10 jaar na het implementeren van de DOTS strategie blijven wereldwijd het aantal tuberculosegevallen toenemen. De HIV pandemie en multiresistente tuberculose vormen enorme uitdagingen voor wereldwijde tuberculosebestrijding, met name in Afrika bezuiden de Sahara en Oost Europa.

Van de 22 landen met de hoogste ziektelast van tuberculosegevallen is Vietnam tot nu toe het enige land dat gedurende de laatste jaren consistent tuberculose-opsporingspercentages en genezingspercentages rapporteert, welke boven de doelstellingen van de WHO liggen [WHO report 2007]. Echter, tuberculose-aangiftecijfers in Vietnam, zoals gerapporteerd aan de WHO, laten geen afname zien. Daarom is Vietnam een belangrijk gebied om het effect van de DOTS strategie op de tuberculose-epidemie in detail te onderzoeken.

De vraag is daarbij of een DOTS programma, dat de WHO-doelstellingen heeft bereikt, voldoende is voor bestrijding van de tuberculose-epidemie. Dit wordt onderzocht door evaluatie van de kwaliteit en de volledigheid van opsporing door het Vietnamese NTP (diagnostisch uitstel onder nieuw gediagnosticeerde sputum-positieve tuberculosepatiënten, toepassing en opbrengst van microscopisch sputumonderzoek naar leeftijd en geslacht,

geografische patronen van de onderzochte proportie van de bevolking welke is onderzocht, respectievelijk welke sputum-positief is), en door beoordeling van het effect van bestrijding op de tuberculose-epidemie (trends in aangifte en jaarlijkse risico op tuberculose-infectie, recidiefpercentage onder succesvol behandelde patiënten met nieuwe sputum-positieve longtuberculose, en prevalentie en trends over tijd van geneesmiddelenresistentie onder tuberculosepatiënten).

Hoofdstuk 2 is een beschrijvend onderzoek, gebaseerd op routinegegevens, over de totstandkoming en ontwikkeling van het NTP in Vietnam gedurende de periode 1986-2000.

Vietnam is één van de 22 landen met de hoogste tuberculoseziektelast wereldwijd. Het NTP Vietnam introduceerde de DOTS aanpak in 1989 en bereikte 100% dekking in het jaar 2000. Sinds 1996 bedraagt de proportie sputum-positieve gevallen welke worden gedetecteerd en behandeld met "short course" chemotherapie meer dan 70%, en zijn de gerapporteerde genezings-percentages met het 8-maands behandelregime consistent hoger dan 85%. Dit toont aan dat de DOTS aanpak haalbaar is in een laag-inkomen land met een hoge ziektelast. Echter, de tuberculose-aangiftecijfers in Vietnam nemen niet af.

In hoofdstuk 3 is het diagnostisch uitstel onderzocht in een dwarsdoorsnede-onderzoek van alle gedurende één kwartaal opeenvolgend geregistreerde patiënten met nieuwe sputum-positieve longtuberculose die werden behandelend door het NTP. Patiënten werden aan de hand van een voorgecodeerde gestructureerde vragenlijst geïnterviewd.

Gemiddeld was, op nationaal niveau in Vietnam, het diagnostisch uitstel kort. Dit betrof het totale uitstel in diagnose en behandeling, het door de patiënt veroorzaakte uitstel (patiënt-uitstel) en het uitstel veroorzaakt door de gezondheidszorgaanbieder (aanbieder-uitstel). Het mediane (spreiding) totale uitstel bedroeg 4 weken (1-48), het mediane patiënt-uitstel 3 (1-48) weken, en het mediane aanbieder-uitstel 1 (0-25) week. Desondanks rapporteerde 15% van de patiënten een totaal uitstel van ≥12 weken en dit vertegenwoordigde 49% van het cumulatieve aantal uitstelweken. Initiële consultatie van een private zorgaanbieder had aanzienlijk effect op de lengte van uitstel, maar met duidelijke regionale verschillen binnen het land.

In hoofdstuk 4 worden toepassing en opbrengst bepaald van microscopisch sputumonderzoek door het NTP, evenals de variatie hierin naargelang leeftijd en geslacht met nadruk op sexeverschillen in toegang tot gezondheidszorg. Hiertoe werd een dwarsdoorsnede-onderzoek uitgevoerd op basis van registers van tuberculoselaboratoria in een aselecte steekproef van 30 districten in het noordelijke deel van Vietnam.

In dit onderzoek bedroegen het aantal van tuberculose verdachte patiënten, en het aantal microscopische sputumpreparaten, welke moesten worden onderzocht teneinde één sputum-positief geval te vinden, 9.7 respectievelijk 29.3. Het percentage van tuberculose verdachte gevallen dat sputum-positief was bedroeg 10.3%. De man-vrouw verhouding was 1,36:1 onder van tuberculose verdachte patiënten, en 1,89:1 onder sputum-positieve tuberculose patiënten. Dit doet eerder vermoeden dat de tuberculose-incidentie hoger is onder mannen,

dan dat vrouwen een slechtere toegang hebben tot tuberculosediagnostiek. Het onderzoek van een derde microscopisch preparaat zou kunnen worden weggelaten.

In hoofdstuk 5 wordt de variatie geëvalueerd in aantallen van tuberculose verdachte gevallen en aangegeven tuberculosepatiënten. In een dwarsdoorsnede-onderzoek werden retrospectief gegevens verzameld uit de registers van alle districtstuberculoselaboratoria in Vietnam over een periode van één kwartaal. Hierbij werd van alle patiënten bij wie onderzoek was verricht het dorp of stadsdeel van herkomst bepaald.

Het totale jaarlijkse aangiftecijfer van sputum-positieve tuberculose bedroeg 78 per 100.000 bevolking; 9 per 1000 had een microscopisch sputum onderzoek. De aangiftecijfers per 100,000 bevolking waren hoger in het zuiden en het midden dan in het noorden van het land. Geografische verschillen in aangiftecijfers weerspiegelden grotendeels werkelijke epidemiologische verschillen in het voorkomen van tuberculose in Vietnam. Aangiftecijfers varieerden aanzienlijk naar geografische breedtegraad, regio en mate van verstedelijking en waren op dorps of stadsdeelniveau niet geassocieerd met armoede of etniciteit. De afstand tot het district gezondheidscentrum was een belangrijke determinant van de toegang tot tuberculosediagnostiek, hetgeen onderdiagnose doet vermoeden in gebieden die verder van gezondheidscentra verwijderd liggen.

In hoofdstuk 6 worden de trends geschat in het jaarlijkse risico op tuberculose- infectie (ARTI) met herhaalde tuberculine-onderzoeken, en worden deze vergeleken met trends in tuberculose-aangiftecijfers, beide in 6 sentinelprovincies waar de DOTS strategie in de jaren ’80 van de vorige eeuw werd geïntroduceerd.

Over de periode 1996-2003 daalden de voor leeftijd en geslacht gestandaardiseerde aangiftecijfers met 2.5 tot 5.9% per jaar in 5 provincies. Aangiftecijfers in de leeftijdsgroep 15-24 jaar namen over deze periode echter significant toe met 4.5 tot 13.6% per jaar in 4 provincies. De gemiddelde leeftijd van nieuw gediagnosticeerde sputum-positieve patiënten nam toe tot 1995, maar daalde daarna weer. De ARTI vertoonde een significante jaarlijkse afname in 3 provincies: één(met 4.9% per jaar) in surveys gehouden tussen 1986 en 1997, en 2 (met 6.6.% en 14.7% per jaar) in surveys gehouden tussen 1993 en 2002. De ARTI vertoonde geen significante afname in de overige 3 provincies.

In hoofdstuk 7 worden de overleving en bacteriologisch bewezen recidiefpercentages bepaald onder patiënten met nieuwe sputum-positieve longtuberculose, 12-24 maanden na voltooide behandeling. Gegevens werden verzameld van een patiëntencohort in een aselecte steekproef van 32 districten in het noordelijke deel van Vietnam.

Onder 304 geïncludeerde patiënten bedroeg het bacteriologische bewezen recidiefpercentage 5%, en was 4% gestart met herbehandeling. Vier van de 12 kweek-positieve recidiefgevallen (33%) had multiresistente tuberculose. In totaal bedroeg het recidiefpercentage 9.9%. Dit was niet hoger dan verwacht op basis van resultaten van een klinisch trial met de behandeling met het 8-maandsregime.

In hoofdstuk 8 worden de resultaten gepresenteerd van onderzoek naar resistentie. Dit onderzoek werd uitgevoerd door verzameling van sputummonsters van opeenvolgend gediagnosticeerde patiënten met sputum-positieve tuberculose in een aselecte steekproef van 40 openbare tuberculoseklinieken in het zuiden van Vietnam. *M. tuberculosis* isolaten werden getest op gevoeligheid voor eerstelijns chemotherapeutica.

Onder nieuwe patiënten bedroeg de prevalentie van resistentie tegen tenminste één middel 26%, en de prevalentie van meervoudige (multidrug) resistentie 1.8%. Onder eerder behandelde patiënten was dit 63%, respectievelijk 23%. Over de voorgaande 6 jaar was de prevalentie van resistentie tegen tenminste één middel significant afgenomen, en was de prevalentie van meervoudige resistentie onder nieuwe sputum-positieve patiënten niet toegenomen, dit in afwezigheid van tweedelijns behandeling. De conclusie is dat, onder deze omstandigheden, een DOTS programma in staat is de ontwikkeling van resistentie tegen antituberculosemiddelen beperkt te houden.

In hoofdstuk 9 worden de belangrijkste bevindingen en beperkingen bediscussieerd, en worden de implicaties van deze studies voor tuberculose bestrijdingsprogramma's en aanbevelingen voor verder onderzoek besproken.

De conclusie luidt dat de tuberculosebestrijding in Vietnam niet het verwachte effect op de tuberculose-epidemie heeft gehad. In deze initiële, indirecte onderzoeken werden geen belangrijke problemen gevonden met betrekking tot de gerapporteerde opsporings- and genezingspercentages. Echter, meer directe evaluaties van de gevalsopsporing en behandelingsuitkomsten zijn nodig. De toename onder adolescenten vraagt om een specifieke verklaring.

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**ABBREVIATIONS**

| | |
|---|---|
| AFB | acid fast bacilli |
| AIDS | acquired Immune-deficiency syndrome |
| aOR | adjusted odds ratio |
| ARTI | annual risk of tuberculoous infection |
| ART | anti-retroviral therapy |
| ARV | anti-retroviral |
| BCG | bacilli Calmette-Guéri |
| CDR | case detection rate |
| CHC | commune Health Centers |
| CHP | commune Health Posts |
| CI | confidence interval |
| CNR | case notification rate |
| CPRGS | Comprehensive Poverty Reduction and Growth Strategy |
| CXR | chest x-ray |
| DHC | District Health Centers |
| DOT | direct observed treatment |
| DOTS | Direct Observed Treatment Short course |
| DST | drug susceptibility testing |
| DTU | District tuberculosis unit |
| EM | ethnic minority |
| EQA | external quality assessment |
| GDP | gross domestic product |
| HCMC | Ho Chi Minh City |
| HCP | health care provider |
| HIV | human Immunodeficiency Virus |
| IUATLD/UNION | International Union Against Tuberculosis and Lung Disease |
| IVDU | intravenous drug user |
| MDG | Millennium Development Goals |
| MDR | multidrug resistance resistant |
| MDR-TB | multidrug resistance resistant tuberculosis |
| MOH | Ministry of Health |
| MOTT | *mycobactera other than Tuberculosis* |
| MTB | *mycobacterium tuberculosis* (*M. tuberculosis)* |
| NTP/NTPV | National TB Control Programme (of Vietnam) |
| NTRL | National TB Reference Laboratory |
| OR | odds ratio |
| PLHA | people living with HIV/AIDS |
| PNT | Pham Ngoc Thach Hospital |
| PPM DOTS | public–private mix for DOTS |
| PTB | pulmonary tuberculosis |
| PTC | provincial Tuberculosis coordinator |
| RMRL | Regional Mycobacterial Reference Laboratory |
| SCC | short-course chemotherapy |

| | |
|---|---|
| SS/ss | sputum smear |
| STI | sexually transmitted infections |
| TB | tuberculosis |
| TST | tuberculin skin test |
| UNAIDS | United Nations AIDS program |
| VND | Viet Nam Dong |
| WHO | World Health Organization |
| XDR-TB | extensively drug-resistant tuberculosis |
| ZN | Ziehl-Neelsen |
| - | negative |
| + | positive |

**ABBREVIATION OF TUBERCULOSIS DRUGS**

| | |
|---|---|
| E, EMB | ethambutol |
| H, INH | isoniazid |
| S, SM | streptomycin |
| R, RIF | rifampycin |
| Z, PZA | pyrazinamid |

**TUBERCULOSIS TREATMENT REGIMENS**

*Long-course*
$3SHZ/6S_2H_2$
$3HRE/6H_2R_2E_2$

*Short-course*
2SHRS/6HE
$2SHRZE/1HRZE/5H_3R_3E_3$

Numbers before the letters indicate the duration in months of the treatment phase; numbers in subscript indicate the number of times the drugs are taken each week.