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KAI BLÖNDAL

Tuberculosis in Estonia with special emphasis on drug-resistant tuberculosis: Notification rate, disease recurrence and mortality

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Tuberculosis in Estonia with special emphasis on drug-resistant tuberculosis: Notification rate, disease recurrence and mortality

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Department of Pulmonary Medicine, University of Tartu, Estonia

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications (I–IV), which are referred to in the text by their Roman numerals:

I. Blöndal K. Barriers to reaching the targets for tuberculosis control: multidrug-resistant tuberculosis. Bull World Health Organ 2007; 85(5): 387–390.

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ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
AMK	Amikacin
CM	Capreomycin
CS	Cycloserine
DOTS	Directly observed short-course
DST	Drug susceptibility testing
EMB	Ethambutol
ERLTM	Estonian Reference Laboratory of Tuberculosis and Mycobacteriosis
ETH	Ethionamide
ETR	Estonian Tuberculosis Registry
FLD(s)	First-line drug(s)
GDP	Gross domestic product
GLC	Green Light Committee
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
ICD	The International Statistical Classification of Diseases and Related Health Problems
INH	Isoniazid
KM	Kanamycin
MDR-TB	Multidrug-resistant tuberculosis
NTP	National Tuberculosis Programme
OXF	Ofloxacin
PAS	Para-aminosalicylic acid
PDR-TB	Polydrug-resistant tuberculosis
PTB	Pulmonary tuberculosis
PTH	Prothionamide
RMP	Rifampicin
SLD(s)	Second-line drug(s)
SMI	Swedish Institute for Infectious Disease Control
SMR	Standardized mortality ratio
STM	Streptomycin
TB	Tuberculosis
VR	Vital registration
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis
Z	Pyrazinamide

I. INTRODUCTION

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis*. The common source of the disease is an infectious person who, by sharing common air space, infects the other one. The most effective way to stop the spread of TB is early identification of the infectious cases and immediate treatment. However, the progression from TB infection to development of the disease and further to cure or death depends on the etiologic agent, host organism, clinical management and socio-economic factors (1), which all should be counted in the management of TB.

In 2011, the World Health Organization (WHO) estimated the incidence as 8.7 million cases of TB globally. During 2011, approximately 1.4 million people died of TB (2). Most of the cases occurred in the WHO regions of South-East Asia, the Western Pacific and African Region (2). It is recognised that the immunodeficiency virus (HIV) is the major factor fuelling the TB epidemic. Thus, the HIV and TB co-infected patients accounted for 13% of all TB cases in 2011, the highest proportion of them estimated to be among the residents of the WHO African Region. During the same year, 0.99 million deaths occurred among HIV-negative cases of TB and an additional 0.43 million deaths among people with an HIV infection (2).

During the last few decades, drug-resistant TB, a man-made phenomenon, has increased significantly. Annually, around 630,000 patients fall sick with multidrug-resistant TB (MDR-TB) worldwide (2). MDR-TB is defined as TB caused by *M. tuberculosis* resistant *in vitro* to isoniazid (INH) and rifampicin (RMP). MDR-TB takes longer to treat than non-MDR-TB and necessitates use of expensive and less-effective second-line anti-TB drugs (SLDs) (3). In 2011, it was estimated that 3.7% of new TB cases and 20% of retreatment cases had MDR-TB (2). Of the 27 high-MDR-TB-prevalence countries, i.e. those countries where the proportion of MDR-TB among never previously treated cases exceeds 6.5%, 15 were in the WHO European Region, Estonia being one of them (2).

Misuse or mismanagement of SLDs may result in development of strains of extensively drug-resistant TB (XDR-TB), which is *in vitro* resistant to INH and RMP, a fluoroquinolone, and to at least one of the three injectable SLDs (amikacin (AMK), capreomycin (CM), or kanamycin (KM)) (3). By the end of 2011 at least one case of XDR-TB was reported by 84 countries worldwide. It was estimated that approximately 9.0% of all MDR-TB cases have XDR-TB, equivalent to 58,500 cases (4).

After a rapid diagnosis of TB or M/XDR-TB, an effective treatment bringing long-term cure should be initiated as soon as possible to stop the transmission of the infection. The Stop TB a scale-up intervention plan for the period 2011–2015 foresees at least a 90% treatment success rate among drug-susceptible TB and ≥75% among MDR-TB cases (5). In cases of the non-HIV-infected drug-sensitive TB patients, it is possible to achieve 97–99% treatment success rates with an average disease recurrence of less than 5% (6). In 2010,

the global treatment success among the new smear positive TB cases was 87%, whereas in the African Region, where the proportion of persons with TB/HIV co-infection was the highest, reached 82%. Meanwhile, the treatment success among new smear positive cases in the WHO European Region, where elevated MDR-TB rates are a problem, was only 67% (2).

It is known that treatment success is considerably lower among the drug-resistant cases; thus, for the MDR-TB patients the global treatment success was 48% and for XDR-TB patients 33% (2). The particularly deadly liaison of XDR-TB and HIV infection was demonstrated in a study from KwaZulu Natal, South Africa, where 52 of 53 (98.1%) patients with XDR-TB and HIV co-infection died (7).

Provided the treatment is effective, TB recurrence has been shown to be moderate in cases of drug-sensitive TB. According to a systematic review of 16 studies (8), the disease recurrence after successful treatment ranged from 0–14%. However, there is a significantly higher risk of TB recurrence and mortality among TB and HIV co-infected persons (9). Little is known about the recurrence rate among MDR-TB patients after successful treatment (10) and none of the studies is of a countrywide-design.

It is acknowledged that TB, HIV, smoking and alcohol abuse are closely related, fuelling epidemics exacerbated by interacting factors (11, 12). HIV, smoking and alcohol abuse are risk factors for TB infection, disease and mortality. All of the four mentioned pose a major public health challenge, as well as torment at the individual level.

In Estonia, the problem of TB, but also of M/XDR-TB, escalated after the sharp social and economic changes in the 1990's, i.e. the break-up of the Soviet Union. In 1998 the first survey of drug-resistance was carried out in Estonia and a proportion of MDR-TB as high as 10.2% of the new cases was found (13). To address the increasing TB incidence and prevent further escalation of M/XDR-TB, the Estonian National TB Control Programme (NTP) was established in 1998.

The present series of studies was undertaken to evaluate the impact of M/XDR-TB on TB incidence, disease recurrence and mortality and to identify the causes of death of TB and M/XDR-TB patients in Estonia and subsequently identify ways to effectively decrease TB and M/XDR-TB incidence and to increase the survival rate of individual TB patients.

2. REVIEW OF THE LITERATURE

The review of the literature touches upon the origin and definitions of TB, the Stop TB Strategy and summarises TB and M/XDR-TB occurrence globally and in Estonia. Incidence, treatment, disease recurrence and mortality of TB and drug resistant TB are dealt with.

2.1. Origin and definition of TB, MDR-TB and XDR-TB

The causative agent of TB, *M. tuberculosis*, is as old as 3 million years (14). The oldest known human remains showing signs of TB are 9,000 years old (15). It has been estimated that in the early 19th century, 30% of all deaths under 50 years of age in Europe could have been attributed to TB (16). Disappointingly, only as late as in January 1944, the discovery of the anti-TB drug streptomycin (STM) was announced (17). A few months before, in March 1943, a proposal to manufacture a para-amino salt of aspirin as an anti-TB agent was presented by Lehmann in Sweden (17). The first treatment with para-amino salicylic acid (PAS) was initiated in October and with STM in November 1944 (17). With the introduction of anti-TB drugs, a hope appeared to win over the disease. Meanwhile, already in 1948, in trials in Great Britain (18) and later in the United States (19), it was shown that resistance to STM had emerged. Putting this into context with our present knowledge, the resistance to STM was most probably due to monotherapy of patients with this agent, novel at that time.

The spontaneous occurrence of drug-resistant mutants among wild strains of *M. tuberculosis* has been well described (20, 21). Nonetheless, it is considered that the drug resistance is primarily a man-made phenomenon, i.e. caused by inadequate or poorly administered treatment regimens that enable drug resistance to develop (3).

The hypothesis of how the resistance to anti-TB drugs may develop was introduced by Mitchison (22). In his paper, Mitchison described three modes of action of anti-TB drugs:

1) Prevention of drug-resistance – a drug of high activity is able to prevent growth of the entire bacterial population in the lesions throughout chemotherapy. A drug of low activity fails to be as suppressive and may allow growth of mutant bacilli;
2) Early bactericidal activity – the ability of anti-TB drugs to kill most of the live bacilli during first two days of treatment. By doing so, the number of bacteria and therefore, the number of possible mutations, will decrease;
3) Sterilizing activity – ability to kill all of the bacilli in the lesions as rapidly as possible. Sterilizing activity measures the speed with which the last few viable bacilli are killed.

In 1948, it was demonstrated that combined chemotherapy, i.e., using more than one drug simultaneously, could appreciably prevent the emergence of drug-resistance (23). Furthermore, it was deemed necessary to ensure that all prescribed doses of combination therapy were actually taken by the patients. In 1960, the British Medical Research Council developed a fully supervised chemotherapy routine to ensure patient adherence to the prescribed treatment regimen. Over twenty years passed before the International Union against Tuberculosis and Lung Disease gradually implemented fully supervised chemotherapy under programmatic conditions in Tanzania and other African countries in the 1980s (24). Meanwhile, more drugs were introduced for treatment of TB and, unfortunately, further resistance developed.

In 1998, Mitchison (25) went on describing four mechanisms of development of resistance in case of poor compliance during short course chemotherapy. The mechanisms were:

1) Bactericidal effect during initial killing – resistance emerging during first days of interrupted treatment due to selection of spontaneously occurred mutations;
2) Mono-therapy during sterilisation of special populations – selection of resistant bacilli from special populations of semi-dormant organisms, with only one anti-TB drug having action in them;
3) Sub-inhibitory drug concentrations during re-growth – in this case the resistant bacilli will grow faster than sensitive;
4) Bacteriopausal effects during re-growth – the selective growth of drug-resistant mutants during the period, when no drugs are taken.

It is known that in case the bacilli are resistant to the two most potent first-line anti-TB drugs (FLDs), INH and RMP, the patient is very difficult to cure and this form of TB is demarcated by a special name, MDR-TB. Since the 1990's highly or extremely resistant bacilli, resistant to six or more drugs, have been reported (26–28). In those cases, the treatment success was worse (56.0%) (27) than in the case of drug-sensitive TB (97–99%) (6), and even worse than that of MDR-TB (66.2–70.2%) (29). In 2005, a provisional definition of extensive drug resistance was first introduced (30). In 2006 WHO convened and revised the provisional XDR-TB case definition (31). The current definition of XDR-TB states that it is a form of TB in which bacilli is resistant *in vitro* to INH, RMP, a fluoroquinolone and to at least one of three injectable SLDs (AMK, CM, or KM).

The increasing number of reports of high prevalence of drug resistance and lack of novel anti-TB drugs has given rise to pessimistic thoughts on the future of TB control. In that context, a question has been posed; exactly how transmittable are these resistant strains compared to drug-sensitive strains. In 2009, Borrell and Ganneux (32) reviewed available studies on infectiousness, reproductive fitness and evolution of drug-resistant *M. tuberculosis*. They concluded that the transmissibility was variable, being from 10 times more (33) to 10 times less (34) transmittable, and could depend on two major aspects:

1) Relative fitness compared to the drug-sensitive strains – likelihood to survive and reproduce. This could be varying based on the strain's genetic background;
2) "Fitness cost" – a reduced growth of resistant strains due to the impact of the mutations on the normal function of the genes. Nevertheless, even if the drug-resistant strains are of decreased relative fitness due to the occurred mutations, in some cases, the drug-resistant strains, after initial reduction of fitness, undergo compensatory evolution and regain their fitness.

Based on these theories, certain mathematical models lead to a possibility that, given time, a fit MDR-TB strain may nonetheless replace the drug-sensitive strain (35). Other models conclude that the future spread of drug-resistant strains is not that alarming because the resistance is often associated with reduction in bacterial fitness (36). Dye (37) has brought forward the hypothesis of severe and benign epidemics. A severe epidemic, illustrated by an example of Russia during the period 1999–2005, is characterised by a self-sustaining epidemic of drug-resistant strains. Dye et al. (36) reviewed the trends of MDR-TB incidence rates among new cases in 10 high-MDR-TB-countries, including Estonia. They concluded that in those settings the reproduction of INH-resistant and MDR-TB strains was less than that of the sensitive strains, representing a benign TB epidemic. Furthermore, as resistant strains are likely to occur due to mutations developing within the sensitive strains and resistant mutants are less fit than the sensitive ones, the production of resistant strains could be decreased by stopping the spread of regular TB (37). This finding led to the conclusion that the current diagnostic and treatment strategies can still result in elimination of MDR-TB. There is, however, a contradiction to the hypothesis of a benign epidemic in Estonia, as Krüüner et al. (38) found that the prevailing TB strain spreading in Estonia belongs to the Beijing genotype family with a high probability (11.5%) of being MDR. More importantly, this strain was found to be at least as transmissible as other strains (32, 38). It is not known which type of TB and MDR-TB epidemic is prevailing in Estonia, therefore one of the aims of the current study was to assess the notification rates of both TB and MDR-TB in Estonia.

2.2. Occurrence of TB and M/XDR-TB

The WHO has been collecting TB case notification data since 1997 (39) from all its Member States, other countries and territories in order to assess the burden of disease and its trend worldwide. In 2012, a total of 182 out of 194 Member States reported TB-related data to the WHO. In Estonia the TB data have been collected throughout the last century but aligned to the international recommendations since 1998.

2.2.1. Global occurrence of TB and M/XDR-TB

In 2011, there were an estimated 8.7 million incident cases of TB (range 8.3–9.0 million), accounting for 125/100,000 (range 120–130) globally. Most of the cases occurred in the WHO regions of South-East Asia, the Western Pacific (59%) and Africa (26%) (2). About 2.9 million cases (range 2.6–3.2 million), equivalent to 33.3% of all cases, occurred among women. The proportion of TB cases co-infected with HIV was estimated to be 13%, with the highest proportion in the African Region, which accounts for 79% of all TB cases among people living with the HIV infection. Globally, the incidence rate/100,000 has been falling since 2001; from 2010 through 2011, it declined by 2.2%.

In 2011, around 0.99 million deaths (range 0.84–1.1 million) occurred among HIV-negative cases of TB and an additional 0.43 million deaths (range 0.40–0.46 million) among HIV-positive people, being equivalent in total to 14 deaths/100,000 (range 12–17) (2). Approximately 1.4 million people died of TB in 2011. A total of 0.3 million deaths occurred among HIV-negative and 0.20 million among HIV-positive women. Globally, the mortality rates have fallen by more than one-third since 1990.

From 1994, anti-TB drug-resistance data have been collected worldwide by the WHO and the International Union against Tuberculosis and Lung Disease within the Global Projects on Anti-Tuberculosis Resistance Surveillance. Reports have been published in 1997, 2001, 2004 and 2008; the last one includes data from 77 countries or settings (40). After that, the yearly WHO global TB reports include data on drug resistance. Already in 1994, drug resistance was reported in almost every country surveyed. Annually, 630,000 patients (range 460,000–790,000) fall ill with MDR-TB worldwide (2). In 2011, it was estimated that 3.7% (95% confidence interval, CI 2.1–5.2%) out of new TB cases and 20% (95% CI 13–26%) of retreatment cases have MDR-TB (2). The probability of MDR-TB was more than 10-fold higher among previously treated patients (40). However, globally, only 4% of new cases and 6% of retreatment cases are actually tested for MDR-TB. In 2012, out of the 27 high-MDR-TB-prevalence countries where the proportion of MDR-TB exceeded 6.5% among never previously treated cases, 15 belonged to the WHO European Region. The highest reported values of MDR-TB among the new cases were in Belarus (32.3%), followed by those in Estonia (22.9%) (2). The WHO estimates that 60% out of the global MDR-TB burden lie in China, India, the Russian Federation, and South Africa.

By the end of 2011, the presence of XDR-TB was reported by 84 countries. It was estimated that globally, approximately 9.0% (95% CI 6.7–11.2%) of all MDR-TB cases have XDR-TB, which is equivalent to 58,500 cases (4). However, the data on XDR-TB are incomplete because the low-income countries do not always have well equipped laboratories to perform drug susceptibility testing (DST) against SLDs.

In 2011, only 4.3% of all TB cases emerged in the WHO European Region (2). The estimated incidence rate was 42/100,000 (range 39–45), which equals

380,000 cases (range 350,000–400,000), including 23,000 (range 20,000–25,000) TB/HIV co-infected cases. Between 2010 and 2011, the TB incidence decreased by 8.5%; however, no data were available on the annual decrease of TB incidence in Estonia. The highest rates of difficult-to-treat M/XDR-TB are found in Europe. It is estimated that 15.1% (range 10–20%) of all new cases and 44% (range 40–49%) among all retreatment cases have MDR-TB, meanwhile, only 56% of new and 27% of retreatment cases were tested for MDR-TB in 2011. In the same year, 32,348 laboratory-confirmed MDR-TB cases were reported to the WHO, of which 10,290 were new and 12,097 were retreatment cases (2). It is estimated that 5% among the detected MDR-TB cases are XDR-TB in the WHO European Region (41). As much as 12% of MDR-TB cases died in Europe in 2011. Among all TB cases the estimated mortality rate was 5.0/100,000 (range 4.9–5.1).

2.2.2. Occurrence of TB and M/XDR-TB in Estonia

In Estonia, TB persists as a major problem, both, at the level of individual patients, as well as at the national level. During the 20th century the highest notification rate was recorded in 1953, with 417 new and relapse cases/100,000. By 1991, the time of the breakdown of the Soviet Union, the TB notification rate had decreased to the lowest level, 25.9/100,000. From 1993, as a result of the so-called transition shock characteristic of most of the Central and Eastern European countries, an increase was observed. Thus, by 1998, the notification rate almost doubled, being 59.4/100,000 (Figure 1). Throughout the last decade, the notification rate has steadily decreased below the level of that in 1991, being 25.4/100,000 in 2011. This is also the lowest recorded TB notification rate in Estonia.

From 2001, retreatment cases other than relapses are included in the case notification (Figure 1); however, the number of these retreatment cases is not large, adding only 1.7/100,000 in 2011.

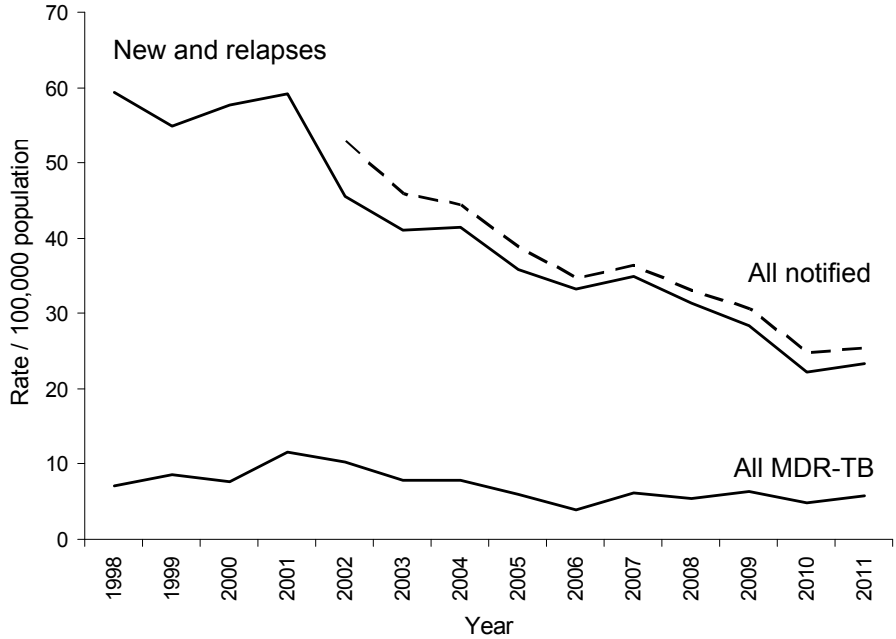

Figure 1. Tuberculosis (TB) notification rate in Estonia, 1998–2011: all new cases and relapses, all notified cases (including all new and all retreatment cases) and all multi-drug-resistant (MDR-TB) cases.

Beginning in the 1960's, information on drug resistance has been available in the laboratories in Estonia; although the first survey was carried out only in 1994 (13) to find 10.2% of MDR-TB among new and 19.2% among previously treated cases. Following that, routine anti-TB drug resistance surveillance was established. During the last decade the notification rate of MDR-TB has been relatively stable, but the proportion of MDR-TB among all TB cases has increased, while the overall TB notification rate has decreased (Figures 1 and 2). In 1998 the MDR-TB notification rate among all TB cases was 7.1/100,000 and in 2011, 5.8/100,000. Among the new pulmonary TB (PTB) cases, the MDR-TB notification rate was 4.3 and 3.5/100,000, respectively. Meanwhile, in 1998, the proportion of MDR-TB cases among the culture-confirmed new PTB cases was 13.9% and in 2011 the proportion reached the alarming level of 23.4%. Among retreatment cases, the proportion of MDR-TB was 35.0% in 1998 and 53.6% in 2011 (Figure 3), whereas the notification rate was 2.6 and 2.2/100,000, respectively. Little is known about the factors possibly influencing the TB and M/XDR-TB epidemic in Estonia.

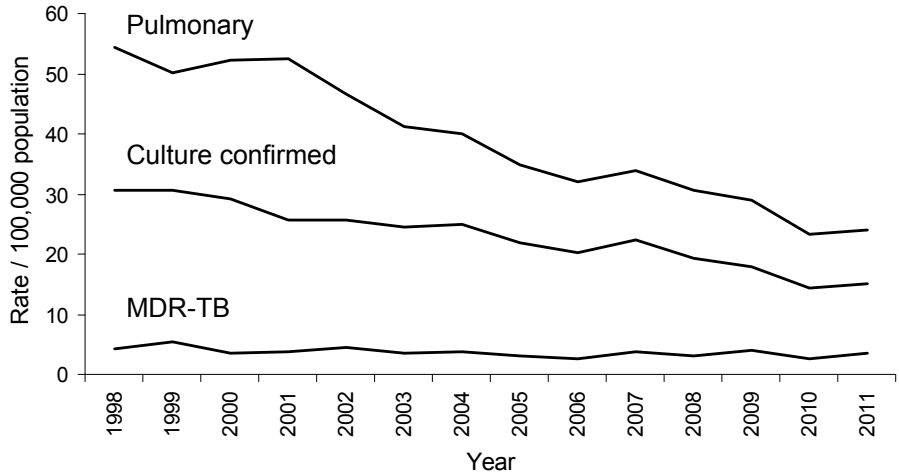

Figure 2. Tuberculosis (TB) notification rate in Estonia, 1998–2011: all new pulmonary TB cases; new culture- confirmed pulmonary TB cases and new pulmonary multidrug-resistant TB (MDR-TB) cases.

The DST to SLDs has been systematically performed since 2001. The proportion of XDR-TB cases among the new pulmonary MDR-TB cases was 10.0% (5 out of 50) in 2001 and 8.5% (4 out of 47) in 2011. Among the retreatment cases, the proportion of XDR-TB was significantly higher, being 34.0% (35 out of 103) and 33.3% (10 out of 30), respectively. In 2011, the notification rate of all XDR-TB cases was 1.3/100,000.

Since 2001 there has been an HIV epidemic in Estonia, resulting in a steady increase of notified HIV and TB co-infected cases (Figure 4). The first HIV-positive TB case was notified in 1999, but by 2011, the number was 46 (3.4/100,000), accounting for 12.7% of all notified cases. The proportion of HIV-positive cases among MDR-TB cases was 19.2% (15 out of 78), translating into a notification rate of 1.1/100,000, which was comparable to that of XDR-TB.

In 2010, 10% of new pulmonary TB patients died during the treatment course in Estonia (2). However, little is known about the specific causes of death.

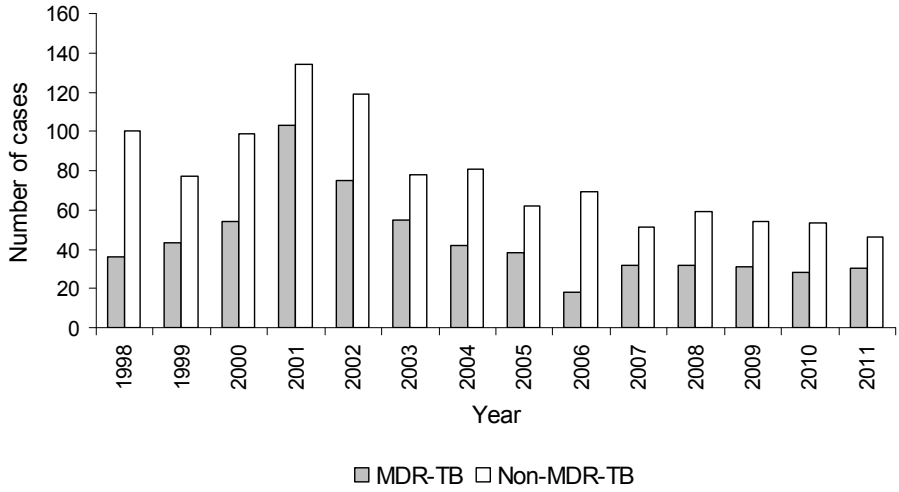

Figure 3. Tuberculosis (TB) cases in Estonia, 1998–2011: all multidrug-resistant TB (MDR-TB) cases and non-MDR-TB retreatment cases.

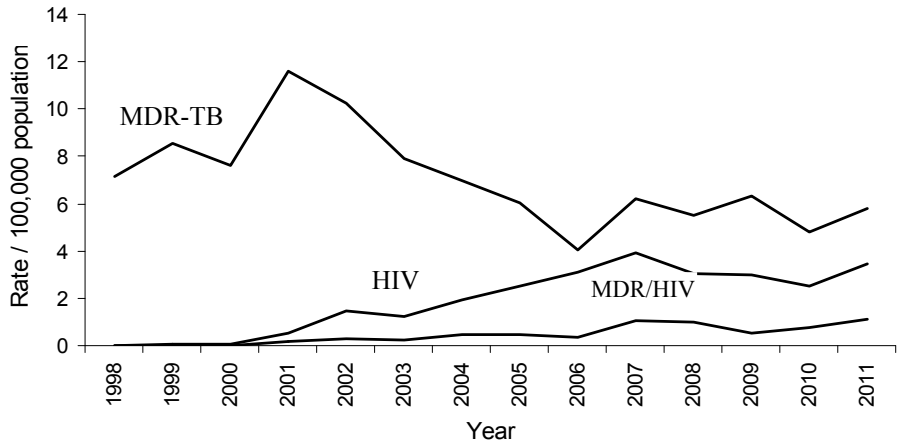

Figure 4. Tuberculosis (TB) notification rate in Estonia, 1998–2011: all multidrug-resistant TB (MDR-TB) cases, all human immunodeficiency virus (HIV) cases and all MDR-TB and HIV co-infected cases.

2.3. Stop TB strategy

To decrease global TB incidence rates and to prevent development of drug resistance in 1994 WHO developed the Directly Observed Short-course (DOTS) strategy (42) as a package of five elements, aimed at achieving at least 70% case detection and 85% cure rate.

The five elements of DOTS include (43):

1) Political commitment with increased and sustained financing;
2) Case detection through quality-assured bacteriology;
3) Standardised treatment with supervision and patient support;
4) An effective drug supply and management system;
5) Monitoring and evaluation system and impact measurement.

The initial DOTS framework has subsequently been expanded to a fundamental pillar of the Stop TB strategy, which itself consists of six elements (44):

1) Pursue quality DOTS expansion and enhancement;
2) Address TB/HIV, MDR-TB and other challenges;
3) Contribute to health system strengthening;
4) Engage all care providers;
5) Empower people with TB and communities;
6) Enable and promote research.

In 2011, 182 WHO Member States out of a total of 194 reported on the progress achieved in TB control (2). The Stop TB targets set for 2012 and 2050 are to reduce prevalence and death rates by 50% compared to their levels in 1990 and to reduce the global incidence rate of active TB cases to less than 1 case per million population per year. However, globally not all countries and regions will achieve the WHO-set targets; therefore, one of the aims of our study was to assess the barriers to reaching the targets globally and specifically in the WHO European Region, which includes Estonia.

In 2000, the WHO and the Stop TB Partnership launched an initiative, the Green Light Committee (GLC), to support countries to manage MDR-TB and to prevent development of further drug resistance. The GLC's role was to review applications from countries and projects wishing to purchase concessionally-priced SLDs and determine whether such projects would be in line with the WHO guidelines (45). Such projects were eligible for technical assistance provided by members of the GLC.

In 1998, the Estonian NTP adopted the DOTS strategy with all five components and reached a countrywide expansion by 2000. The first five-year TB programme for the period 1997–2003 aimed at decreasing TB incidence among new cases to 30/100,000 population by 2005. The current, third five-year TB programme aims at decreasing TB incidence among new cases to 20/100,000. In 2001, due to the alarmingly high rate of MDR-TB and the lack of SLDs to treat these patients, the NTP applied to the GLC for the countrywide project on management of MDR-TB, which started on the 1st of August 2001. The

technical support has been provided to the NTP by WHO and The International Union against Tuberculosis and Lung Diseases. Furthermore, technical and financial support has been provided by the Finnish Lung Health Association, the joint project of the Non-Governmental Organizations in the Nordic Countries, the Centers for Disease Control and Prevention, Atlanta, USA, and the Open Estonia Foundation. From 2001 onward all TB-related services in Estonia have been funded from domestic sources (2).

Currently, the effect of the countrywide availability of the SLDs on incidence of TB, as well as MDR-TB, has not been evaluated either globally or in Estonia. Therefore, one of the aims of our study was to evaluate the impact of the countrywide availability of SLDs on the TB and MDR-TB incidence.

2.4. Incidence of TB and M/XDR-TB

TB incidence depends on the presence of the source of infection and transmission of the infection in the society (1). To interrupt the chain of transmission the source should be eliminated (diagnosed and treated) as soon as possible. There are numerous challenges on the way to the elimination of TB and M/XDR-TB. The risk factors for being exposed to infection, for developing the disease after being infected and for mortality, are largely overlapping. This section presents a short overview of the known risk factors.

2.4.1. Risk of developing TB and M/XDR-TB disease

Following an infection with *M. tuberculosis* the host organism has approximately 10% lifetime risk of developing TB disease, with half of the risk falling within the first 5 years following the infection (1). The risk of TB among HIV-positive persons is much higher, up to 5–10% annually (1), as the HIV infection impairs cell-mediated immunity. Among 2,737 newly HIV-seroconverted South African gold miners, the incidence of TB doubled within the first year of HIV infection (adjusted risk ratio, ARR 2.1; 95% CI 1.4–3.1) (46).

HIV infection not only aids the progression of a TB infection into disease, but also increases the severity of the TB disease by undermining granuloma formation, mainly due to impairing the maturation of macrophages in the lungs (47, 48). On the other hand, TB exacerbates the acquired immunodeficiency syndrome (AIDS) by increasing viral replication, where the possible mechanisms include: 1) stimulation of HIV-1 production by inflammatory cytokines, mainly by tumour necrosis factor-α, 2) increasing the expression of chemokine receptors CXRC-4 and CCR5 and 3) down-regulating the chemokine receptor CCL5 (47–49).

In addition to HIV infection, there are multiple other interacting factors influencing the development of TB disease (1, 50, 51):

1) The factors that depend on the host organism like age, sex, ethnicity, body build, and pregnancy;
2) Medical factors: immunosuppressive treatment, renal failure, haemophilia, gastrectomy and jejunoileal bypass, carcinoma, pneumoconiosis (silicosis, coal worker's pneumoconiosis), and diabetes;
3) Genetic factors: human immune response to TB;
4) Environmental factors: poverty, occupation, diet, smoking, alcohol and drug abuse, place of residence (urban vs. rural), etc.;
5) Factors associated with *M. tuberculosis*: infecting dose and strain virulence.

As for the risk factors for developing M/XDR-TB, a review of 29 papers by Faustini et al. (52) concluded that the pooled risk of MDR-TB was 10.23 times higher in previously treated than in never treated cases. The risk estimates were higher in studies carried out in Western Europe (risk ratio, RR 12.63; 95% CI 8.20–19.45) than in Eastern Europe (RR 8.53; 95% CI 6.57–11.06). The patients with MDR-TB were more likely to be foreign born (odds ratio, OR 2.46; 95% CI 1.86–3.24), younger than 65 years (OR 2.53; 95% CI 1.74–4.83), male (OR 1.38; 95% CI 1.16–1.65), and HIV positive (OR 3.52; 95% CI 2.48–5.01). In Estonia, the risk factors for developing MDR-TB were: previous anti-TB treatment (OR 4.11; 95% CI 2.77–6.08), being younger than 65 years of age [24 years or younger (OR 2.57; 95% CI 1.09–6.06), 25–44 years (OR 2.64; 95% CI 1.35–5.16), and 45–64 years (OR 2.06; 95% CI 1.06–3.99)], female sex (OR 6.23; 95% CI 1.02–37.99) and birth outside of Estonia (OR 82.04; 95% CI 3.46–1945.47) (53). The determinants of XDR-TB were: previous anti-TB treatment (OR 10.54; 95% CI, 5.97–18.62), HIV infection (OR 3.12; 95% CI, 1.31–7.41), homelessness (OR 2.73; 95% CI 1.15–6.48), and alcohol abuse (OR 1.98; 95% CI 1.08–3.64) (53).

Once the infectious TB and M/XDR-TB individuals are present in the community and disseminate infection, these factors play a significant role in increasing the number of patients with both active TB and M/XDR-TB disease. Beyond addressing the socio-economic and clinical factors to decrease the risk of contracting infection and developing the disease, it is of pivotal importance to diagnose infectious cases early and provide prompt effective treatment to halt the infectiousness. The impact of the various risk factors listed above on TB and MDR-TB notification in Estonia is not known; therefore one of our studies was designed to evaluate the impact of poverty and HIV on TB and MDR-TB notification rates.

2.4.2. Treatment and recurrence of TB and M/XDR-TB

Besides the immediate treatment success, the effectiveness of the treatment is measured by the rate of TB recurrence after successful treatment. In cases of non-HIV-infected drug-sensitive TB patients with RMP included in the treatment regimen at least in the intensive phase, it is possible to achieve

97–99% treatment success with an average disease recurrence rate of less than 5% (6).

It has been proven that FLDs are not effective in the treatment of MDR-TB. Studies addressing the treatment success among MDR-TB patients using FLDs have found that the treatment success rate was low and the relapse rate was high. In a study from China, MDR-TB patients treated with FLDs had a treatment success of 66–83%, while 57% of patients had disease recurrence during 4 years of follow-up (54). In an 18-month follow-up study of patients treated with FLDs in four districts in Karakalpakstan, Uzbekistan, 6% and 43% mortality and 23.0% and 60.0% disease recurrence were found for TB and MDR-TB, respectively (55).

Management of patients with drug-resistant TB, i.e. mono-resistant, polydrug-resistant (PDR-TB), and particularly M/XDR-TB, is complicated because of the longer treatment, lesser effectiveness of anti-TB drugs and more side effects. Mono-resistance refers to resistance to a single anti-TB drug and PDR-TB refers to resistance to two or more anti-TB drugs but not to both INH and RMP. The patients with M/XDR-TB remain infectious for longer periods as the sputum conversion is slower, the overall treatment success lower and mortality significantly higher than among those with non-MDR-TB (56–59). Furthermore, because of the high cost of the SLDs, the management of M/XDR-TB represents a significant monetary burden for TB programmes (60).

The treatment of MDR-TB cases using internationally recommended treatment regimens with SLDs provides better results. Although noted among patients specially selected for the GLC-project, the treatment success was up to 77% among new and up to 69% among previously treated cases (61). In a meta-analysis by Johnston et al. (62), the pooled treatment success of 27 studies was much lower, 62% (95% CI 57–67), while 11% (95% CI 9–13) of patients died.

In India, MDR-TB patients enrolled on a standardized MDR-TB treatment regimen, i.e. a regimen of same drugs for all patients in a given area, reported a treatment success of 61% (63). In South Korea, the treatment success among MDR-TB patients treated with individualized treatment regimens, i.e. drug regimens tailored according to the DST results, was higher, reaching 73.2% (10). Orenstein et al. (64) compared data on treatment success of individualized vs. standardized treatment regimens from 29 studies. The patients with MDR-TB treated with individualized regimens had a treatment success of 64% (95% CI 59–68%) vs. 54% (95% CI 43–68%), when using standardised regimens, although this difference was not statistically significant. The proportion of those who died during the treatment was 11% and 12%, respectively; again, the difference was not statistically significant.

The treatment success among TB patients is known to be decreasing in the following order: drug-sensitive TB > PDR-TB > MDR-TB > XDR-TB. Thus, in Abkhazia, Georgia, the treatment success of patients with different resistance patterns was compared and it was found that 85.2% of patients with drug-sensitive TB completed the treatment successfully, while those with PDR-TB had a treatment success of 78.3% and those with MDR-TB only 32.3% (65).

Pulmonary MDR-TB and XDR-TB patients treated with individualized treatment regimens in Estonia during the period 2003–2005 had a treatment success of 60.4% and 42.6%, respectively (66). The difference was statistically significant. During the period from 2002 to 2004, a total of 1,027 M/XDR-TB patients were enrolled on individualized treatment regimens in Latvia. The treatment success was 67.9%, with a statistically significant difference between MDR-TB and XDR-TB patients (69.3% and 38%, respectively) (67). In Tomsk, Russia, the difference between the treatment success of MDR-TB (66.7%) and XDR-TB (48.3%) patients was also statistically significant (68). However, the difference between the treatment success of XDR- and MDR-TB patients is not always significant, as for example in Peru, where 66.3% of MDR-TB patients and 60.4% of XDR-TB patients were successfully treated (69). In a study assessing treatment results among XDR-TB patients pooled together from 4 countries/settings, the treatment success was as low as 39.3% (70). The lowest reported treatment success among non-HIV-infected XDR-TB patients was in South Korea, or only 18% (71).

It was mentioned before that the effectiveness of treatment is measured by a stable cure and the aim is to have not more than 5% TB recurrence (6). It has been shown that it is possible to achieve as low as 5% recurrence in case of drug-sensitive TB, but the follow-up time of the majority of studies did not exceed 3 years. According to the 2008 systematic review of 16 studies by Cox et al. (8), the disease recurrence rates after successful treatment ranged from 0–14%. The median follow-up time in these studies ranged from 12 to 31 months. Chang et al. (72) found that out of 12,183 patients with mainly non-resistant pulmonary TB in Hong Kong, 0.9% (95% CI 0.8–1.1%) relapsed within 30 months after commencement of therapy. A study from Spain reported 4.3% TB recurrence among successfully treated predominantly drug-sensitive TB patients after as long as 8-year follow-up (73).

The patients with recurrent disease are known to be at higher risk for M/XDR-TB and mortality, as found by Jeon et al. (71) and, also in a review by Johnston et al. (62). Little is known about the rate and time of recurrence among drug-resistant TB cases. Moreover, none of the studies is of a country wide design. In South Korea, the pooled treatment success of drug resistant cases was 45.3%, or 46.2% among MDR-TB and 29.3% among XDR-TB cases. In that study the total disease recurrence during 3–7 years of follow-up from the beginning of treatment was 8.9%, or 13.6% among XDR-TB and 8.8% among MDR-TB cases (74). In a previously mentioned study from South Korea, the disease recurrence of MDR-TB patients treated with individualized treatment regimens was 4.4% during the median follow-up period of 38.7 months (10). The recurrence of TB after treatment of pulmonary MDR-TB in Peru with a minimum follow-up time of 24 months after treatment was 5.1% (95% CI 3.0–8.2) (75). None of the studies referred to were of countrywide design. In 2001, country wide management of M/XDR-TB was launched in Estonia, but until now no data have been available to determine the long-term effectiveness of the treatment regimens used at that time.

Numerous studies have demonstrated an association between HIV status and TB death. In Brazil, a total of 161,481 drug-sensitive TB patients were evaluated for treatment success, which was 85.7% among HIV-negative and 55.7% among HIV-positive persons, while the mortality was 4.2% vs. 23%, respectively (76). When stratifying mortality by HIV infection in 22 relevant studies, Straetemans et al. (77) found that mortality was significantly higher among HIV-infected drug-sensitive persons compared to non-HIV-infected (9.2% vs. 3.0%). In the Netherlands, Borgdorff et al. (78) found that the HIV-infected TB patients had an increased risk of death compared to non-infected patients (hazard ratio, HR 9.9, 95% CI 5.4–18). In a study by Mallory et al. (9) from South Africa, HIV infection was associated with a significantly higher TB recurrence compared to non-HIV-infected patients (8.2 vs. 2.2 per 100 person-years; multivariate-adjusted incidence RR 4.9, 95% CI 3.0–8.1). Furthermore, HIV-positive patients continue to die more rapidly after completion of anti-TB treatment. In Zomba, Malawi, up to seven years after completing the TB treatment, the HIV-infected patients had higher death rates than the HIV-negative ones (HR 2.2, 95% CI 1.7–2.8) (79). In sub-Saharan Africa, 25.7% of deaths among the HIV-positive patients occurred during anti-TB therapy, while the rest of the deaths (74.3%) occurred during the 2.5-year period after successful completion of anti-TB therapy (80). It is known that the cause of death among the HIV-positive patients after completing TB treatment is most often not TB but rather AIDS-related causes, including *Mycobacterium avium* complex infection, *Pneumocystis jiroveci* pneumonia, non-Hodgkin's lymphoma, etc. (81, 82). This evidence makes it important to ensure early initiation of highly active antiretroviral therapy (HAART) in HIV-infected patients with TB (80, 83, 84).

The death toll is known to be much higher in cases of M/XDR-TB and HIV co-infection. In a cohort of South African MDR-TB patients, 35.2% of HIV-positive died versus 1.62% HIV-negative ones ($P<0.0001$) (85). The particularly deadly liaison of M/XDR-TB and HIV has been demonstrated in a study from KwaZulu Natal, South Africa, where 52 of 53 (98.1%) patients with XDR-TB/HIV co-infection died within 16 days from the time of diagnosis (7). In another study from KwaZulu Natal, HIV co-infection was an independent risk factor for death (adjusted odds ratio, aOR 5.6) among 1,209 MDR-TB patients (86). In Lima, Peru, 57% of HIV-positive individuals (31 out of 52) died on treatment, with a majority of deaths occurring due to MDR-TB (83). However, in that study, individuals receiving HAART showed a lower mortality compared to those without such treatment (HR 0.4 95% CI 0.2–0.9). In Thailand the survival of MDR-TB patients was reduced in case they were co-infected with HIV (HR 11.7; 95% CI 2.1–64.9). In the same study, the absence of HAART was an independent risk factor for death (HR 7.9; 95% CI 1.5–43.1) (87). HAART has been shown to significantly improve not only the survival, but even the overall treatment outcome of HIV-infected XDR-TB patients (88). To conclude, there is an international consensus that an effort should be made to

prevent TB in people with HIV infection and to provide comprehensive HIV care in association with directly observed therapy for TB/HIV (89, 90).

Apart from HIV infection, other risk factors for poor treatment outcome and mortality have been thoroughly studied. Nevertheless, these studies are mainly done either on drug-sensitive TB or with inclusion of all TB cases. Fortunately, during the last decade, there have been several studies available also on MDR-TB. The risk factors for poor treatment outcome and mortality are largely similar to those for TB infection and progression to disease and include: 1) demographic factors: male sex (62, 91–93), older age (78, 80, 91, 94–100), younger age in a low-income country (92); 2) socio-economic and life-style factors: low BMI and hypoalbuminemia (51, 62, 74, 80, 83, 100–102), poverty or social marginalization (51, 100, 102), marital status (102) educational level (51, 100, 102), imprisonment (institutionalization) in the past (100, 102), smoking and air pollution, although it is considered to be more evidence of the relationship between TB disease than association between TB infection and mortality (11, 51, 77, 92, 100, 102–110), alcohol abuse (51, 62, 66, 92, 98, 100, 102, 111, 112), overall co-morbidities (93, 100, 101, 113), HIV infection (7, 11, 62, 64, 83, 100, 114); and 3) TB-related factors: previous anti-TB treatment (62, 66, 71, 74, 98, 115), extent of disease and/or cavitary disease (71, 92, 97, 112, 113), smear positivity at diagnosis (62, 66, 92, 100, 115), smear negative at diagnosis in HIV-infected patients (100), different composition of treatment regimens (64, 116).

2.5. TB and M/XDR-TB mortality

Mortality from TB is an important indicator for monitoring the effectiveness of treatment regimens, but also of the capacity of TB control programmes to diagnose TB and manage the patients. The M/XDR-TB has been associated with high mortality rates during treatment (7–17%) (62, 64, 70), particularly among HIV-infected patients (7, 83), as previously mentioned.

According to the WHO recommendations for TB programmes, the definition for treatment outcomes include definition of death, i.e. a patient who dies from any cause during the course of treatment (117). This definition, however, excludes deaths that occur among TB patients after treatment failure, default from treatment and transfers out, and therefore underestimates the true mortality among TB patients. Furthermore, this definition includes all other causes of death apart from death due to TB itself. In a study by Straetemans et al. (77), the pooled percentage of TB patients dying of TB itself during treatment among HIV-infected persons was 9.2% (95% CI 3.7–14.7%) and among HIV-uninfected persons, 3.0% (95% CI 21.2–7.4%), whereas the pooled percentage of TB patients dying due to any cause during TB treatment was 18.8% (95% CI 14.8–22.8%) and 3.5% (95% CI 2.0–4.92%), among HIV-infected and HIV-uninfected persons, respectively.

To improve the evaluation of the NTP efficiency, it has been proposed to estimate mortality among TB patients recorded in vital registration (VR) systems along with the internationally-recommended standard treatment outcome definitions for TB (118). However, Korenromp et al. (119) has urged using the standard definitions of the causes of deaths in both national VR systems as well as in the cohort treatment outcome reports in a way that would allow both systems to adhere to the International Classification of Diseases and Related Health Problems (ICD-10).

In cases when the VR system is not in place alternative methods should be used. In the sample registration system, events are recorded routinely from a representative sample of the population and demographic surveillance systems using verbal autopsies to assess causes of death (120). However, the reliability of the method of verbal autopsy has been increasingly questioned, as it includes inherent errors, mainly due to the expert errors in determining the cause of death (121, 122). Thus, the cause of death may be recorded differently, depending largely on the subjectivity and training of the experts. For example, a publication from Taiwan by Lu et al. (123) points out that the doctors trained in diverse local and foreign educational systems use different terminology in the native language for the same diagnosis. Sibai (120) in his paper concludes, based on the one by Lenfant et al. (124), that the reporting of causes of death is less accurate, when the death is sudden, attributable to a stigmatized condition, or occurs among certain minorities, social classes and older age groups. In the case of TB, at least three out of these occasions certainly apply.

In 2003 the VR systems of 115 countries, including Estonia, were assessed for timeliness, completeness and coverage of registration and the proportion of deaths assigned to ill-defined causes. The VR system in Estonia was evaluated as being of high-quality with 100% completeness and coverage and only 5% of deaths being coded as ill-defined (125). However, there is also some possible misclassification in the Estonian VR system, as identified in the classification of alcohol poisoning in the mortality statistics (126). In 2011, WHO used for the first time the VR data from 91 countries representing 46% of the deaths caused by TB to estimate the global TB-mortality (90). Those countries had well-functioning VR systems defined as the following: 1) coverage of at least 70% of the population, and 2) ill-defined causes of death (ICD-19 code B46, ICD-10 codes R00–R99) of less than 20% of all registered death (125). In cases when the VR was for some reason incomplete, sample VR systems or mortality surveys were used to obtain direct measurements of TB deaths. Before 2011, the estimates of TB mortality were based on the data from 89 countries, mainly from the European region and regions in the Americas, representing only 8% of the world's TB cases. The improved quality of the data on TB mortality allowed revising the global estimates. Thus in 2010, in total, 1.4 million (range 1.2–1.5 million), including an estimated 0.35 million deaths (range 0.32–0.39 million) among HIV-positive cases occurred due to TB. The WHO estimate published in 2011 was lower than that published in 2010 (1.7 million, including 0.4 million among HIV-positive people) (127).

It is well established that patients with TB have an increased risk of death during and after treatment as compared to the general population. While there are several studies on the standardized mortality ratio (SMR) and causes of deaths during and after TB treatment, there are neither studies addressing specifically M/XDR-TB patients nor studies from countries with a high MDR-TB incidence, like Estonia. A study of fatality in patients with pulmonary TB, diagnosed in England and Wales in 1983 (97) and followed up until the end of anti-TB chemotherapy, found, using standardized rates, that the all cause mortality among people with PTB was 10 times higher than that of the general population. The case fatality in that study was 12.9%. A retrospective survey of TB patients in Liverpool (99) with an 8-year follow-up period revealed that patients previously diagnosed with TB were 4.5 times more likely to die (95% CI 3.7–5.4) than did the general Liverpool population. Furthermore, subjects below 75 years of age had a high mortality from cancer. There are two studies from India with an average follow-up time of 1.6 (92) and 3.3 years (128), respectively. The case fatality was 9.4% in the first and 20.4% in the second study, the all cause mortality compared to the general population was 6.1 (95% CI 5.4–6.9) and 4.2 (95% CI 3.9–4.5) in the urban and sub-rural cohort, respectively. Furthermore, the mortality of TB patients continues to be higher than in the general population even after successful treatment. A 4.5-fold (95% CI 3.42–5.57) excess all cause mortality rate was found among successfully treated drug-sensitive TB patients in a study from southern Ethiopia with an average follow-up time of 3.6 years (91).

Up to now, the causes of the death of TB and MDR-TB patients and their assumed excess mortality compared to the general population has not been evaluated in Estonia, even though this information is important in order to improve the survival of this group of patients, particularly considering that in Estonia, the majority of TB and MDR-TB patients are of working age.

3. AIMS OF THE STUDY

The overall aim was to evaluate the impact of M/XDR-TB on the TB notification rate, disease recurrence and mortality, and to identify the causes of death of TB and M/XDR-TB patients.

The specific aims of the studies were:

Paper I To identify the global barriers to reaching the targets for TB control.

Paper II To evaluate the impact of countrywide management of TB and the availability of SLDs on the notification rates of overall pulmonary TB and MDR-TB, taking into account HIV co-infection and the national economy in Estonia.

Paper III To assess the treatment outcome of the first GLC-approved countrywide management of MDR-TB and XDR-TB in Estonia and to evaluate risk factors contributing to TB recurrence.

Paper IV To assess overall and cause-specific mortality among TB and MDR-TB patients at the diagnosis and after successful completion of treatment compared to the general population in Estonia.

4. METHODS

This section encompasses the study population, definitions, laboratory methods, treatment regimens and modalities of TB and M/XDR-TB management, data collection and statistical methods.

4.1. Study population

This thesis is based on one round table article and the results of three studies which were carried out on partly overlapping cohorts consisting of subjects diagnosed with TB or M/XDR-TB in Estonia during the period January 01, 1998 to December 31, 2009. The partly overlapping cohorts and the different time periods of the studies were determined by the specific aims and timing of the studies. Throughout all the studies the subjects who emigrated were defined as transferred out from Estonia and were excluded from analysis. The Ethics Committee on Human Research at the University of Tartu, Estonia, approved the study protocols.

Paper I

The round table article identifying the main barriers to reaching the targets for TB control in the different regions of the world covered data available from various publications, including the WHO reports on TB, MDR-TB and HIV/AIDS. The population covered by WHO annual reports on TB has been steadily increasing. Thus, only 65 countries or 29% of WHO Member States submitted their data directly to the WHO for the 1993 report (129), while the 2006-WHO report (130), which was the latest assessed document for the Paper, covered 200 out of 211 countries and territories. The reports on drug-resistance included publications on various populations starting from 1943 as well as the WHO reports on anti-TB drug resistance surveillance. The first WHO report on drug resistance (13) summarizes data made available from 35 countries, whereas in the 2004 report (131) data on drug resistance were available from 77 countries or settings (70% of 194 Member States). The Paper included data on notification of TB and MDR-TB in Estonia during the periods January 1, 2000 through December 31, 2000 (131) and the treatment outcome of MDR-TB patients notified in Estonia from August 1, 2001 through December 31, 2001 (61).

Paper II

All subjects from both the civilian and the penitentiary sectors who fulfilled the criteria for PTB diagnosed during the period 1998–2006 were included to evaluate the impact of countrywide management of TB and M/XDR-TB patients on the respective notification rates in Estonia. Patients with extra-

pulmonary TB and retreatment cases other than relapses were excluded from the analyses.

The beginning of the study was determined by: 1) the start of implementation of the DOTS strategy in Estonia in 1998 and 2) launching the country wide management of M/XDR-TB in 2002. The two observation periods (January 01, 1998 through December 31, 2001 and January 01, 2002 through December 31, 2006) were defined to evaluate the effect of the country wide availability of SLDs on TB and M/XDR-TB notification rates.

Paper III

In Paper III the treatment outcome of M/XDR-TB patients as well as recurrence of TB among those successfully treated was evaluated. All subjects diagnosed with active pulmonary or extra-pulmonary M/XDR-TB from both civilian and penitentiary sectors in Estonia during the period August 01, 2001, through July 31, 2003, were included with the exclusion of those who received treatment with SLDs for less than 1 month. The subjects enrolled were followed until December 31, 2010.

Paper IV

The excess mortality and causes of death of all patients diagnosed while alive with new respiratory TB during the period from January 01, 2002 through December 31, 2009 were measured. The subjects included belonged to the age group of 25–64 years and were followed up until death, emigration or until December 31, 2011, whichever event occurred first. Two cohorts were defined: one involved everyone fulfilling the criteria for inclusion and the second was composed only of the successfully treated patients from the former group. The subjects with an unknown survival status at the end of the observation period were excluded (Figure 5). The beginning of the study period (January 01, 2002) coincided with the country wide availability of FLDs and SLDs.

4.2. Definitions

WHO TB and M/XDR-TB case definitions, as well as treatment outcome definitions, were used (132-134). The TB cases were classified as pulmonary or extra-pulmonary. The case definitions used in the studies were as follows:

- New case – a patient who has received no anti-TB treatment or has received it for less than one month.
- Relapse – a patient whose most recent treatment outcome was “cured” or “treatment completed” and who is subsequently diagnosed with bacteriologically positive TB by sputum smear microscopy or culture.

- Retreatment cases other than relapses included treatment after default, treatment after failure, and others. Others were patients who did not fit into any of the above categories.
- Chronic case – a patient who remained smear-, sputum- or culture-positive after completing a retreatment regimen.

The definitions used for recording treatment outcome were:

- Cured: 1) In case of drug-sensitive TB – a patent whose sputum smear or culture was positive at the beginning of the treatment but who was smear- or culture-negative during the last months of treatment and on at least one previous occasion; 2) in case of M/XDR-TB – a patient who has completed treatment and has at least five consecutive negative cultures from samples collected at least 30 days apart during the final 12 months of treatment.
- Treatment completed – a patient who has completed treatment but does not meet the definition for cure because of a lack of bacteriological results.
- Failed: 1) in case of drug-sensitive TB, the treatment is considered to have failed if sputum smear or culture is positive at 5 months or later during treatment, and 2) in case of M/XDR-TB, the treatment is considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy are positive or if any of the final three cultures is positive.
- Defaulted – a patient whose treatment was interrupted for two or more consecutive months.
- Died – a patient who dies for any reason during the course of treatment.
- Successfully treated patients were defined as the sum of patients who were cured and those who completed the treatment. A poor treatment outcome was defined as the sum of treatment failures, defaulters of treatment, and those who died.
- Patient with respiratory TB (IV) – a patient who has TB of respiratory organs, confirmed or not by bacteriological or histological means (ICD-10 A15–A16).
- Bacteriological confirmation of subjects by culture was used instead of that by smear; M/XDR-TB, as well as non-M/XDR-TB was confirmed by DST. Non-M/XDR-TB cases included those with drug-sensitive TB or any pattern of resistance other than M/XDR-TB. The disease recurrence was confirmed by culture without performing genotyping of isolates to differentiate between recurrence caused by the former strain and re-infection.

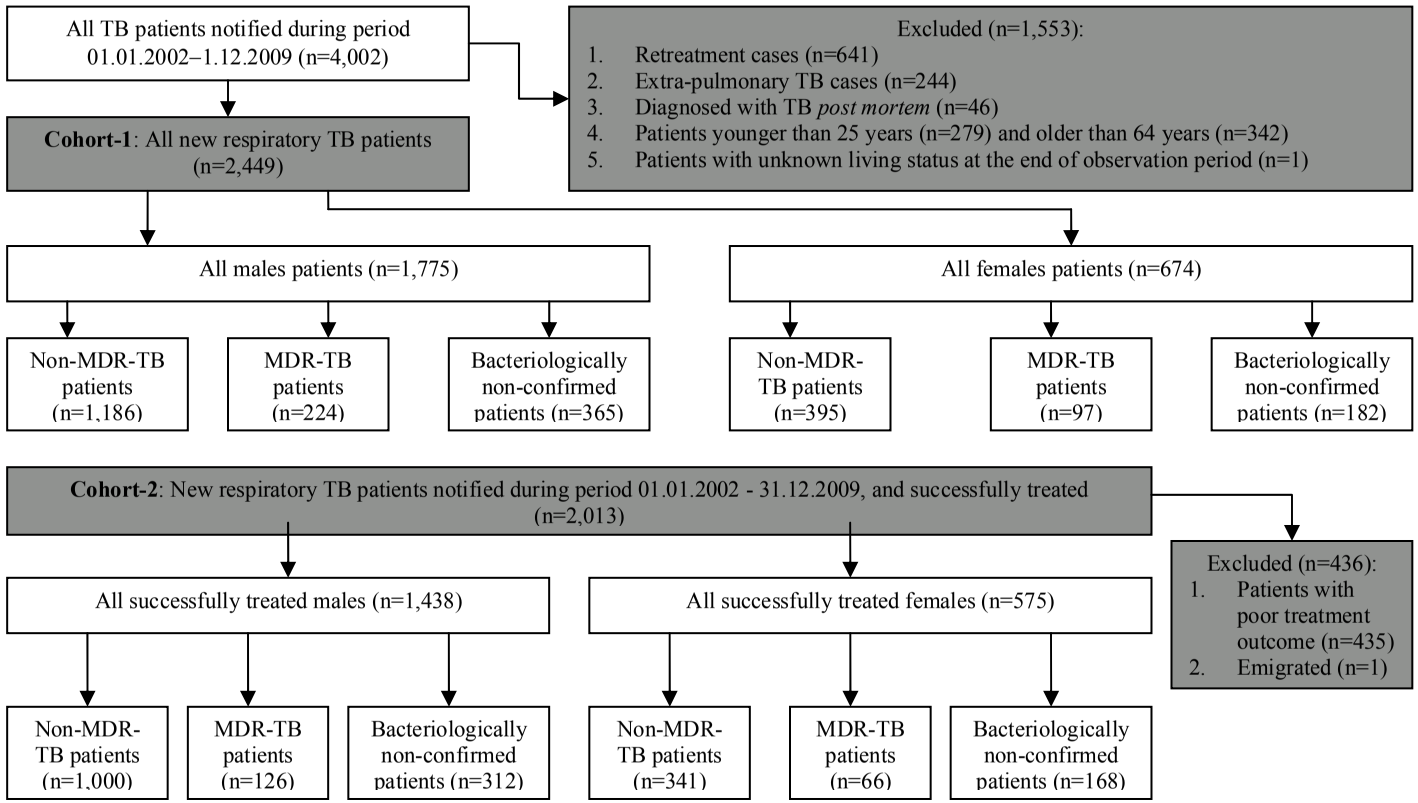

Figure 5. Flow-chart of selection of study population in Paper IV: Cohort 1 included new tuberculosis (TB) patients with respiratory TB and Cohort 2 involved only successfully treated new patients with respiratory TB in Estonia, 2002–2009, by sex. M/XDR-TB: multidrug- and extensively drug-resistant TB.

4.3. Laboratory methods

According to the country policy, at the diagnosis, three smear microscopies had to be performed and at least two samples of a biological material from affected sites were sent for culture and DST to FLDs. In cases when mono-drug-resistance, PDR-TB, or MDR-TB was confirmed, DST to SLDs was done routinely.

From 1997, the TB laboratory network in Estonia has been quality-assured by the supranational reference laboratory, the Swedish Institute for Infectious Disease Control (SMI). From 1998 onwards, culture and DST were routinely performed and recorded. The cultures were performed on conventional Löwenstein-Jensen solid media and in BACTEC® broth media using BACTEC® MIGIT960 fluorometric mycobacterial detection system or BACTEC® MIGIT460 radiometric system (both from Becton Dickinson Diagnostic Systems, Sparks, MD, USA). For identification of species, the AccuProbe TM Rapid DNA Probe Test (Gen-Probe Inc., San Diego, CA, USA) and GenoType® MTBC (Hain LifeScience GmbH, Nehren, Germany) were used. DST was performed by the proportion method using BACTEC® MIGIT460 (Becton Dickinson) for nine drugs: INH (0.2 μg/mL), RMP (2.0 μg/mL), STM (4.0 μg/mL), ethambutol (EMB) (5.0 μg/mL), AMK (2.0 μg/mL), KM (5.0 μg/mL), CPM (5.0 μg/mL), prothionamide (PTH) (5.0 μg/mL) or ethionamide (ETH) (5.0 μg/mL) and ofloxacin (OFX) (2.0 μg/mL). From 2003, the DST for pyrazinamide (Z) (100.0 μg/mL) was performed. Resistance was defined as the presence of growth of >1% of the colonies in the drug-containing media, compared with the growth in the drug-free medium.

Smears were stained with Ziehl-Neelsen method and/or fluorochrome. Competence in performing sputum smear microscopy, culture and DST for INH, RMP, STM and EMB was ensured by quality assurance procedures organised by the Estonian Reference Laboratory of Tuberculosis and Mycobacterioses (ERLTM) and by the SMI. Random verification of DST results for KM, CPM, ETH, AMK and OFX was performed by the SMI.

4.4. Treatment

For the treatment of drug-sensitive and bacteriologically non-confirmed TB cases the internationally recommended standardized short-course treatment regimens, such as category I for new cases and category II for previously treated cases, were used. Commonly, the category I treatment regimen consisted of daily dosing of INH, RMP, EMB and Z for 2 months, followed by INH and RMP once daily three times per week for 4 months. Category II treatment regimen consisted of daily dosing of INH, RMP, EMB, Z and STM, followed by one month of INH, RMP, EMB and Z and 5 months of INH and RMP once daily three times per week.

For treatment of mono-resistant or PDR-TB, the treatment regimens recommended by the Partners in Health (135) were used (Table 1). In case of

M/XDR-TB individualised treatment regimens were designed based on the GLC-approval in 2001:

- The treatment regimen consisted of at least four oral drugs (a fluoroquinolone, PTH, CS, Z) and one of the second-line injectables, KM, CPM or AMK; SM could be used if the strain was confirmed to be susceptible;
- EMB was added if the strain was susceptible;
- Para-aminosalicylic acid (PAS) was added in case of extensive resistance or intolerance of other drugs;
- Agents with an unclear role in M/XDR-TB treatment, such as amoxicillin/clavulanate and clarithromycin, were added in case of poly-resistance to SLDs;
- Injectables, STM, KM, AMK and CPM, were used until 2–3 consecutive months of culture-negative results had been obtained, but not for less than 6 months;
- The total duration of treatment was at least 18 months after bacteriological conversion.

Table 1. Commonly used treatment regimens in case of polydrug-resistant tuberculosis (PDR-TB) in Estonia, 2002–2011

Patterns of drug resistance	Suggested regimen	
	Intensive phase [1]	Continuation phase [1]
INH (± STM)	3 RMP, Z and EMB (± STM)	6 RMP, Z and EMB
INH and Z	6 STM, RMP, EMB and a fluoroquinolone	6 RMP, EMB and a fluoroquinolone
INH and EMB	6 STM, RMP, Z and a fluoroquinolone	6 RMP, Z and a fluoroquinolone
RMP	6 INH, EMB, Z , STM and a fluoroquinolone	6 INH, EMB, Z and a fluoroquinolone
RMP and EMB (± STM)	6 KM, INH, Z, PTH[2] and a fluoroquinolone	12 KM, INH, Z, PTH[2] and a fluoroquinolone
RMP and Z (± STM)	6 KM, INH, EMB, PTH[2] and a fluoroquinolone	12 KM, INH, EMB, PTH[2] and a fluoroquinolone
INH, EMB and Z (± STM)	6 KM, RMP, PTH[2], CS and a fluoroquinolone	12 KM, RMP, PTH[2], CS and a fluoroquinolone

[1] The number indicates the duration of the respective treatment phase with the drugs provided in months. [2] Prothionamide (PTH) and ethionamide (ETH) were interchangeable. AMK: amikacin; CPM: capreomycin; CS: cycloserine; EMB: ethambutol; INH: isoniazid; KM: kanamycin; PAS: para-aminosalicylic acid; RMP: rifampicin; STM: streptomycin; Z: pyrazinamide.

The treatment regimens were slightly different from the 2011-WHO M/XDR-TB guidelines (84), where longer use of an injectable agent (minimum 8 months) and use of a newer generation of fluoroquinolone, such as levofloxacin and moxifloxacin instead of ofloxacin was recommended. From 2006, levofloxacin as the preferred fluoroquinolone agent replaced ofloxacin in the treatment regimens in Estonia.

The treatment of non-MDR-TB patients was carried out under direct observation six times per week during the intensive phase (i.e. first 2–3 months of treatment) and three times per week during the continuation phase. Treatment of M/XDR-TB patients was directly observed six times per week during the whole treatment course. However, in cases where the SLDs were administered twice per day, then only the first daily dose was given under direct supervision. All patients were receiving social support in the form of food parcels and transportation support to and from the health care centre, which equalled to an average USD 2.5 per day.

4.5. Data collection

To create the study-specific databases, the TB-related data for the three studies (II–IV) were extracted from the Estonian Tuberculosis Registry (ETR) database. The ETR database is continuously updated from standardized NTP forms completed by the physicians and nurses involved in management of TB patients. The study data were reviewed by the principal investigator with an assistance of the ETR personnel and physicians responsible for patient management to verify the results and to complete the missing data. The data on drug resistance and smear and culture results were obtained from the ERLTM. For calculation of the incidence and mortality rates, the mid-year population was downloaded from the Statistical Office of Estonia (136). The data on HIV infection in Estonia originated from the Health Board (137). Follow-up for death or emigration was carried out at the Estonian Mortality and Population Registries by using a unique personal identification number and/or name date of birth, and place of residence. The causes of death, which to our prior judgment, could be affected by residual TB sequelae, anti-TB treatment or known behavioural risk factors for TB disease (50), such as smoking and alcohol abuse, were chosen in order to analyse the mortality of TB and M/XDR-TB patients (IV). Due to the possible misclassification of alcohol poisoning in the mortality statistics, which is recognized in Estonia (126), the selected alcohol-related causes of deaths like mental and behavioural disorders due to alcohol abuse (F10 according to the ICD-10), alcoholic cardiomyopathy (I42.6), alcoholic liver disease (K70) and accidental poisoning by and exposure to alcohol (X45) were grouped together. The cancers, which, according to the International Agency for Research on Cancer (138) are affected by alcohol, included cancers of the oral cavity (C01–C08), pharynx (C09–C14), oesophagus (C15), colon (C18), rectum (C19–C21), liver (C22), larynx (C32) and female breast (C50).

The smoking-related cancers included cancers of the oral cavity (C01–C08), pharynx (C09–C14), oesophagus (C15), stomach (C16), colon (C18), rectum (C19–C21), liver (C22), pancreas (C25), nose and sinuses (C30–C31), larynx (C32), bronchus and the lungs (C34), cervix uteri (C53), ovary (C56) and urinary organs (C64–C68) and myeloid leukaemia (C92) (138).

The data on gross domestic product (GDP) per capita in purchasing power standards were obtained from Eurostat (139) and expressed in current international dollars (II).

To analyse the risk factors for disease recurrence (III), the variables were arranged into five groups: 1) demographic and socio-economic factors that included sex, age, place of birth, marital status, education, housing, employment status, history of imprisonment and health insurance; 2) factors related to baseline clinical history that included the way of case finding, i.e. active case finding by the health care workers or passive case finding or self-referral by the patient, time from the diagnosis to current treatment, history of previous use of anti-TB drugs, belonging to the group of chronic patients, TB localization, bacteriological status at the time of diagnosis, and presence or absence of a cavity in the lungs; 3) drug-resistance stratified by individual drugs (including resistance to ETM, OFX and thioamides and resistance to all three second-line injectable agents); 4) different resistance groups (including the total number of resistant drugs tested, XDR-TB and MDR-TB); 5) factors related to treatment that included duration of treatment in months, inclusion of an injectable agent into the regimen, SLDs being stopped due to the side effects, the number of drugs given in the intensive phase, the number of drugs given in the continuation phase and inclusion of any of the following drugs: a fluorquinolone, thioamide, CS, PAS or Z into the regimen.

Codes of the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), were used for assessing the excess mortality and causes of death of subjects (IV) as well as for assessing the risk factors contributing to TB recurrence (III).

The TB-related data for the round table article (I) for identification of main barriers to reaching the targets for TB control were taken from the literature, including WHO reports on TB, M/XDR-TB and HIV/AIDS (13, 18, 19, 23, 24, 26, 31, 39, 42, 43, 61, 130, 131, 140-144) and ETR.

4.6. Statistical analysis

For analysing the data for the three Estonia-based Papers (II–IV), the SPSS® statistical package, version 17.0 (Statistical Package for Social Sciences, Chicago, IL, USA), was used. The Visual FoxPro 6.0 (Microsoft Corporation, Redmond, WA, USA) and Stata 10 (StataCorp LP, College Station, TX, USA) were used to calculate the excess mortality and determine the causes of death of all patients diagnosed alive with new respiratory TB (IV). In case of missing

data, the analyses were performed only for the cases with complete sets of information.

Time trends in the overall notification rates and notification rates of culture confirmed pulmonary TB were tested using the Cochran-Armitage test for trend (II). Linear regression analysis was used to assess the impact of the availability of the SLDs and changes in GDP per capita on the change in yearly TB notification rates, as well as to evaluate the influence of HIV infection on the PTB and M/XDR-TB notification rates (II).

Cox regression analysis with the Wald statistical criteria and backward elimination method were used to estimate the predictors of TB recurrence and mortality among all diagnosed M/XDRTB patients as well as among successfully treated ones (III). Both univariate and multivariate analyses stratified by XDR-TB patients were performed. To demonstrate the probability of TB recurrence, the Kaplan-Meier method was used, whereas the difference between strata was assessed with Breslow's test (III).

The SMR was calculated for males and females separately by dividing the observed number of deaths by the expected number of deaths (IV). The expected number of deaths in the cohorts was calculated by multiplying the age- and sex-specific person-years by the corresponding national mortality rates. The calculation was stratified by two calendar periods, 2002–2006 and 2007–2011. The 95% CI for SMR was calculated assuming a Poisson distribution for the observed deaths. Multivariate Poisson regression models were used to estimate the effect of age (45–64 vs. 25–44 years), education (basic or less vs. higher or secondary), ethnicity (non-Estonian vs. Estonian) and MDR-TB (MDR-TB vs. non-MDR-TB) on the risk of death.

5. RESULTS

The main results of Papers I–IV are summarised in this section. In Paper I the barriers to reach the targets laid out for global TB control were assessed by WHO regions. Paper I enabled to placing Estonia in the context of global TB and M/XDR-TB control. Paper II assessed the TB and MDR-TB notification trend and selected determinants of disease. Treatment outcome and disease recurrence of M/XDR-TB were the subject of the Paper III. Paper IV analysed the overall and cause-specific mortality among TB and M/XDR-TB patients as compared to the general population.

Paper I

By the end of 2004, 83% of the world's population lived in countries or parts of countries covered by DOTS. Treatment success among 1.7 million DOTS patients notified in 2003 averaged 82%, which was close to the 2005 global target of 85%. However, the treatment success was below average in the African Region (72%), as well as in the European Region (75%). The main identified barrier to reach the global target was TB/HIV co-infection in the WHO African Region and drug-resistance in the WHO European Region (130).

In 2004, Estonia belonged to the top ten countries or areas with the highest proportion of MDR-TB among never-previously-treated cases (12.2%) (Figure 6). In addition to Estonia, five more high-MDR-TB-prevalence countries or regions originated from the former Soviet Union: Kazakhstan (14.2%); the Tomsk oblast in the Russian Federation (13.7%); Karakalpakstan, Uzbekistan (13.2%); Lithuania (9.4%) and Latvia (9.3%) (130, 145). The reported highest values of MDR-TB among previously treated cases were in Oman (58.3%) and Kazakhstan (56.4%), followed by Lithuania (53.3%), Estonia (45.3%), the Tomsk oblast in the Russian Federation (43.6%), the Orel oblast in the Russian Federation (42.4%), Karakalpakstan in Uzbekistan (40.2%), Egypt (38.2%) and Henan in China (36.6%) (130, 145).

Estonia was one of the five first GLC-approved countries for management of MDR-TB. The treatment success among the first 46 MDR-TB patients enrolled for treatment from August 1, 2001 through December 31, 2001 was 65.2% (30/46). Meanwhile, the pooled treatment success of the first five GLC-approved projects (Estonia, Latvia, Manila in the Philippines and the Tomsk oblast in the Russian Federation) was as high as 70%, or 78% among the never previously treated patients and 69% among previously treated patients (61).

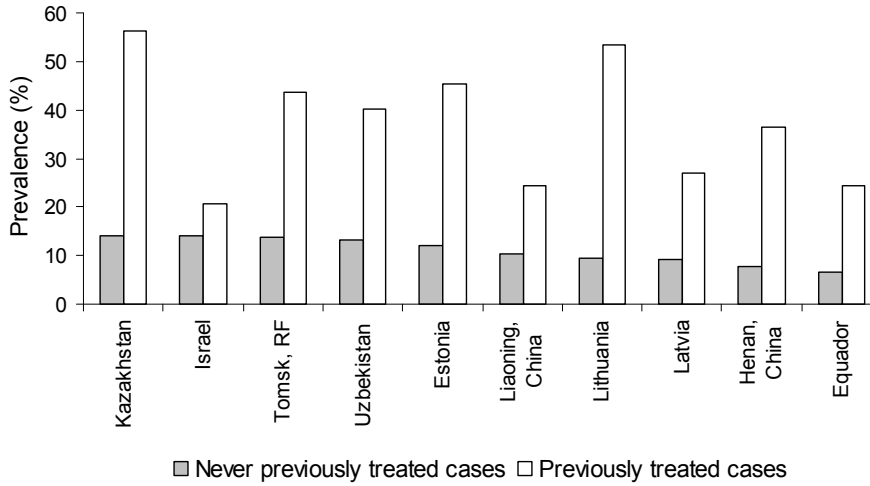

Figure 6. Prevalence of multidrug-resistant tuberculosis (MDR-TB) in the ten countries or areas with the highest MDR-TB prevalence. RF: Russian Federation (modified from I).

Paper II

A total of 5,196 new and relapse pulmonary cases were included in the study, of whom 3,725 (71.7%) were males. The mean age of all subjects was 45.9 years. A total of 3,862 study subjects (74.3%) had DST results. Of those with the available DST results, 760 cases (19.7%) were diagnosed as having MDR-TB. Starting in 2000, 541 of MDR-TB strains (98.8%) were tested against SLDs and of theses, 95 (17.6%) were confirmed as having XDR-TB. Since 2001, 99.6% of patients (3,033 of 3,045) have been tested for HIV and of these, 132 (4.4%) have been HIV-positive.

During the period 1998–2006 the incidence of TB decreased from 59.2/100,000 in 1998, when the NTP was launched, to 32.7/100,000 in 2006, resulting in a mean annual decrease of 3.3 cases/100,000 or 7.02% (P=0.007). During the same period, the notification rate of M/XDR-TB decreased from 6.7 to 3.5/100,000, resulting in a mean annual decrease of 1.7 cases/100,000 (5.5% yearly, P=0.008). During the whole study period (1998–2006), a significant increase in GDP per capita occurred, together with a lowering of the notification rate of overall TB, as well as that of MDR-TB (P<0.001 and P<0.001, respectively) (Figure 7). At the same time, there was an increase in TB/HIV co-infection, which had a negative impact on the notification rates (P<0.001 and P=0.001, respectively) (Figure 8).

The availability of SLDs after 2002 did not have any significant impact on the case notification rates of M/XDR-TB as compared to the previous period (1998–2001). However, there was a significant accelerating impact of the availability of SLDs on the decline in the annual notification (Figure 9).

During 1998–2006 the mean treatment success rate among all PTB cases increased from 72.7% to 77.4% (P=0.009), whereas there was a decrease among the MDR-TB cases, from 54.8% to 51.1% (P=0.018). Meanwhile, the mean pooled treatment success of XDR-TB (47.7%) was much lower than that of all PTB and MDR-TB patients. Due to the low number of XDR-TB cases, it was not possible to analyse the treatment success over the years.

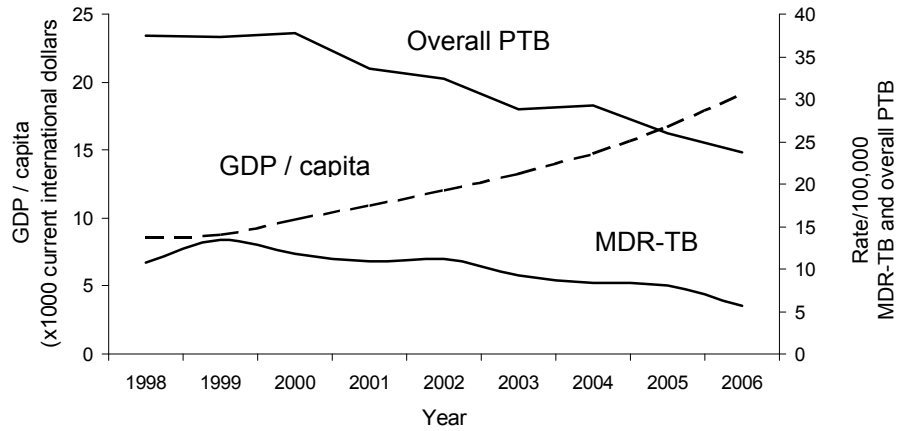

Figure 7. Notification rate of overall (new and relapses) culture-confirmed pulmonary tuberculosis (PTB) and multidrug-resistant TB (MDR-TB) in correlation with the Gross Domestic Product (GDP) per capita expressed in current international dollars per year in Estonia, 1998–2006. One international dollar equals one USD at a given point in time (modified from II).

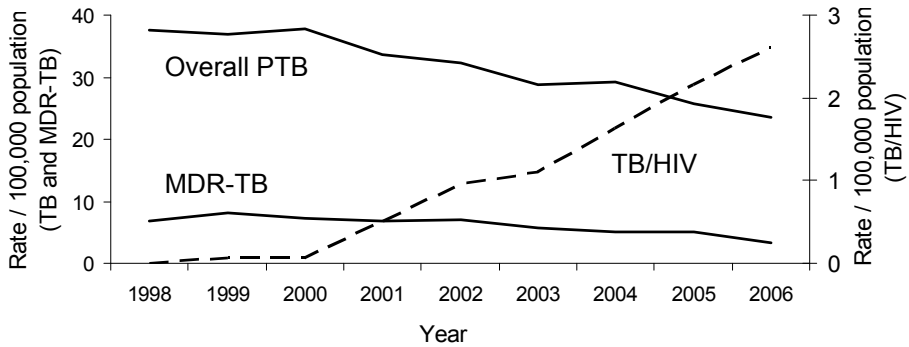

Figure 8. Notification rate of overall (new and relapses) culture-confirmed pulmonary tuberculosis (PTB) and multidrug-resistant tuberculosis (MDR-TB) patients in correlation with that of TB and human immunodeficiency virus (HIV) co-infection in Estonia, 1998–2006 (modified from II).

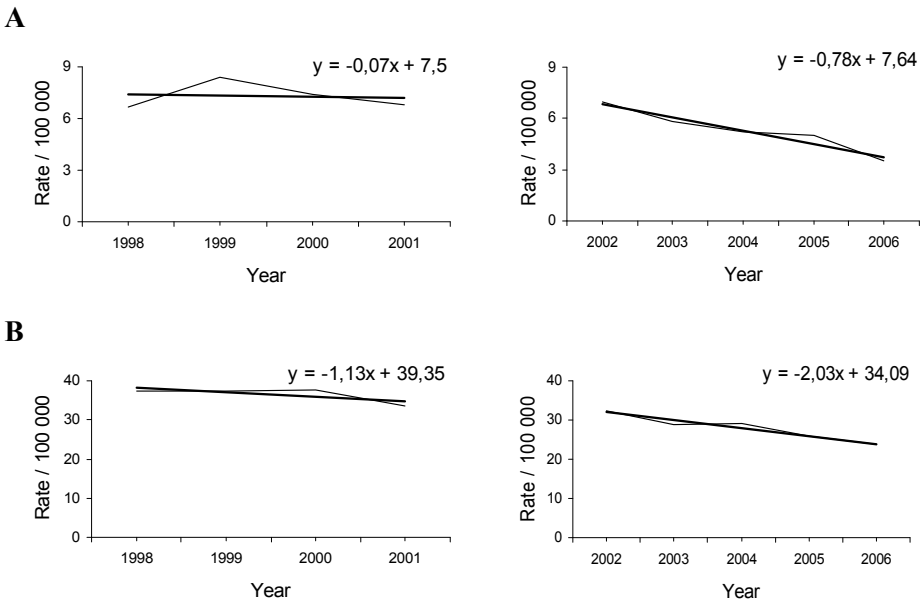

Figure 9. Time trends in the notification rates of culture-confirmed pulmonary tuberculosis (TB) in Estonia, 1998–2006, before and after second-line drugs (SLD) became available in 2002: A) for multidrug-resistant TB (MDR-TB) and B) for overall pulmonary TB. The time trends, tested by the Cochran-Armitage test, were non-significant for MDR-TB and overall pulmonary TB during both tested periods (1998–2001 and 2002–2006). Linear regression analysis using the availability of SLDs as a covariate showed a significant accelerating impact on the down-going trends in MDR-TB (P=0.025), as well as in overall pulmonary TB (P=0.003) (modified from II).

Paper III

A total of 211 patients diagnosed with MDR-TB during the period from August 01, 2001 through July 31, 2003, were included; out of these 43 patients had XDR-TB. The median age of all subjects was 42.9 years (range 17–76), 154 (73.0%) were males and 172 (81.5%) were Estonians. A total of 5 (2.5%) HIV-positive cases were diagnosed out of the 197 subjects tested for HIV infection.

The treatment was successfully completed by 129 patients (61.1%). Treatment success among the MDR-TB and XDR-TB patients was 63.1% and 53.5%, respectively. The median duration of treatment among the successfully treated patients was 19.8 months (range 6.1–53.7). Out of all successfully treated patients, 11 (8.5%) had relapsed by the end of the follow-up time. A total of 82 patients (38.9%), including 20 patients with XDR-TB, had a poor treatment outcome: 47 (22.3%) defaulted, 18 (8.5%) failed treatment and 17 (8.1%) died.

The median follow-up time of all study subjects from the start of treatment with SLDs until the disease recurrence, death, emigration, or December 31, 2010, whichever date was earlier, was 98.1 months (range 2.1–125.7 months). By the end of the observation period, 38 patients (18.0%) had died of TB and 23

(10.9%) of other reasons. The cumulative recurrence-free survival was lower among XDR-TB patients than among MDR-TB patients (P=0.012) (Figure 10).

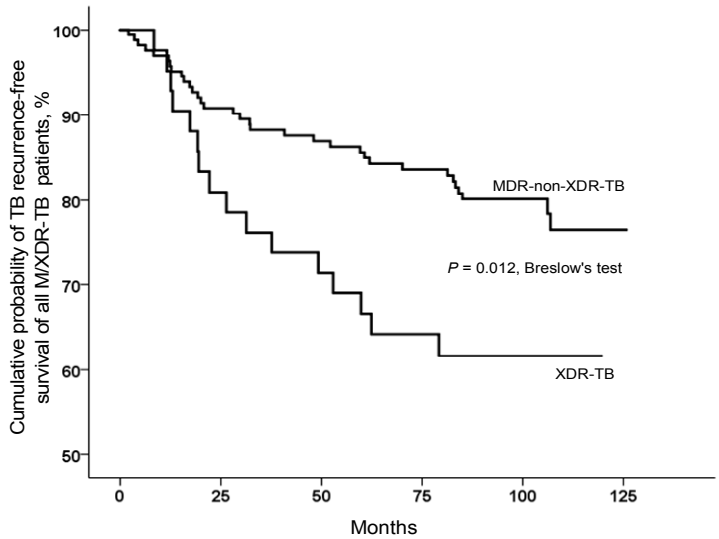

Figure 10. Cumulative probability of tuberculosis (TB) recurrence-free survival of the 211 multidrug-resistant- and extensively drug-resistant TB (M/XDR-TB) patients, who started treatment in Estonia, 01.08.2001–31.07.2003, stratified by XDR-TB (n=43) and MDR-TB patients (n=168). Reproduced with permission from III.

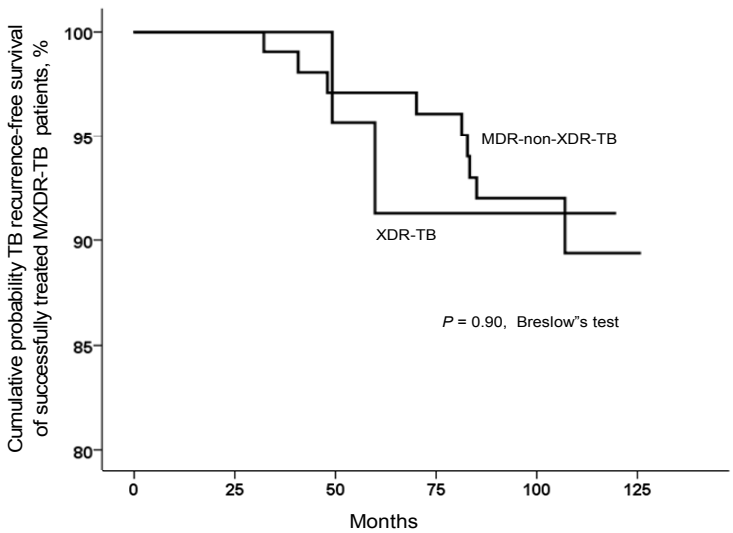

Figure 11. Cumulative probability of tuberculosis (TB) recurrence-free survival of the 129 successfully treated multidrug-resistant- and extensively drug-resistant TB (M/XDR-TB) patients, who started treatment in Estonia, 01.08.2001–31.01.2003, stratified by XDR-TB (n=23) and MDR-non-XDR-TB (n=106). Reproduced with permission from III.

There was no difference between the 129 successfully treated XDR-TB (n=43) and MDR-TB patients (n=168) in terms of the cumulative recurrence-free survival (Figure 11). The median time to TB recurrence was 70.1 months (range 32.3–106.9). However, the probability of recurrence peaked during the period from year 5 to year 7 (63.6%) of follow-up. Of all patients with a successful treatment outcome, 118 (91.5%) remained without active TB, eight (6.2%) died of other reasons; 11 (8.5%) had a TB recurrence.

In a multivariate model the risk factors associated with TB recurrence for all included patients were male sex, birth outside Estonia, history of previous anti-TB treatment, sputum smear positivity at the beginning of treatment, resistance to >4 anti-TB drugs, resistance to all three second-line injectable and the absence of an injectable agent from the treatment regimen ($P<0.05$ for all). On the other hand inclusion of PAS in the regimen and a greater number of drugs given during the continuation phase of treatment appeared to be protective against TB recurrence ($P<0.05$) (Table 2).

Among all successfully treated patients, only a history of previous TB treatment was a risk-factor for TB recurrence (HR 4.28, 95% CI 1.13–16.15, $P=0.032$). The median length of treatment among the 11 patients, who later developed TB recurrence, was 20.2 months (range 18.2–36.2); the difference was not statistically significant for those 118 patients who stayed TB free (median 19.7 months; range 6.1–53.7).

In a multivariable model, including all 43 XDR-TB patients, male sex ($P=0.007$), birth outside Estonia ($P=0.041$), a history of previous anti-TB treatment ($P<0.001$), sputum-smear-positivity at the start of treatment with SLDs ($P=0.021$), resistance to >4 TB drugs ($P=0.033$) and the absence of an injectable drug from the treatment regimen ($P=0.009$) were found to have a negative impact on TB recurrence, whereas the higher number of anti-TB drugs given during the continuation phase ($P<0.001$), the presence of PAS ($P=0.010$) and OFX ($P=0.037$), and non-interruption of any of the SLDs due to their side effects ($P=0.029$) were protective against recurrence (Table 2). No significant risk factors were found, when the covariates were stratified by XDR-TB among the 129 successfully treated patients in a multivariable model.

Table 2. Risk factors for disease recurrence in all patients (n=211) with M/XDR-TB, who started treatment with second-line anti-tuberculosis drugs (SLDs) in Estonia, 01.08.2001–31.07.2003 (reproduced with permission from III)

Characteristic		M/XDR-TB patients	Crude HR (95% CI)	P-value	Adjusted HR[1] (95% CI)	P-value	Adjusted HR[1] (95% CI)	P-value
		n (%)	All M/XDR-TB patients				Stratified by XDR-TB	
Demographic and socio-economic								
Sex								
	Male	154 (73)	0.26 (0.10–0.65)	0.004	3.58 (1.41–9.10)	0.007	3.61 (1.42–9.15)	0.007
	Female	57 (27)	Reference		Reference		Reference	
Age[2]		42.9 (17–76)	1.02 (0.99–1.04)	0.095	–	–		
Place of birth								
	Other[3]	39 (18.5)	2.45 (1.35–4.43)	0.003	2.10 (1.14–3.86)	0.018	1.91 (1.03–3.53)	0.041
	Estonia	172 (81.5)	Reference		Reference			
Marital status								
	Single or divorced	117 (55.5)	0.81 (0.47–1.41)	0.46	–	–	–	–
	Married or cohabitation	94 (44.5)	Reference					
Education								
	Elementary	80 (37.9)	1.33 (0.77–2.32)	0.31	–	–	–	–
	University, college, manual school	131 (62.1)	Reference					
Housing								
	No permanent place of living	17 (8.1)	0.68 (0.21–2.19)	0.52	–	–	–	–
	Permanent place of living	194 (91.9)	Reference					
Employment status								
	Unemployed	76 (36.0)	1.29 (0.74–2.26)	0.37	–	–	–	–
	Employed	135 (64.0)	Reference					
History of imprisonment								
	Yes	63 (29.9)	1.10 (0.61–1.99)	0.75	–	–	–	–
	No	148 (70.1)	Reference					
Health insurance								
	No	85 (40.3)	1.02 (0.58–1.77)	0.96	–	–	–	–
	Yes	126 (59.7)	Reference					

Table 2. *(Continued)*

Characteristic	M/XDR-TB patients	Crude HR (95% CI)	P-value	Adjusted HR[1] (95% CI)	P-value	Adjusted HR[1] (95% CI)	P-value
	n (%)	All M/XDR-TB patients				Stratified by XDR-TB	
Factors related to baseline clinical history							
Ways of case fining							
Active case finding	49 (23.2)	0.84 (0.43–1.64)	0.61	–	–	–	–
Passive case finding	162 (76.8)	Reference					
Time to current treatment from MDR-TB diagnoses (months)[2]	1.0 (-11–196)	1.01 (1.002-1.02)	0.015	–	–	–	–
History of previous anti-TB drugs use							
Previously treated	110 (52.1)	4.44 (2.21–8.90)	<0.001	4.34 (2.17–8.71)	<0.001	3.96 (1.94–8.07)	<0.001
Never received anti-TB drugs	101 (47.9)	Reference		Reference		Reference	
Belonging to group of chronic patients							
Yes	25 (11.8)	2.88 (1.53–5.42)	0.001	–	–	–	–
No	186 (88.2)	Reference					
TB localization							
Pulmonary and any other site	203 (96.2)	21.47 (0.48 –9597.58)	0.33	–	–	–	–
Extra-pulmonary	8 (3.8)	Reference					
Bacteriological status at the time of diagnosis							
Sputum smear positive	118 (55.9)	2.38 (1.28–4.40)	0.006	2.15 (1.16–4.00)	0.016	2.07 (1.11–3.86)	0.021
Sputum smear negative	93 (44.1)	Reference		Reference		Reference	
Cavity in the lung							
Yes	161 (23.7)	2.16 (0.97–4.79)	0.060	–	–	–	–
No	50 (76.3)	Reference					
Drug resistance stratified by individual drugs							
Resistance to ethambutol							
Yes	198 (93.8)	3.25 (0.45–23.55)	0.24	–	–	–	–
No	13 (6.2)	Reference					

Table 2. *(Continued)*

Characteristic	M/XDR-TB patients	Crude HR (95% CI)	P-value	Adjusted HR[1] (95% CI)	P-value	Adjusted HR[1] (95% CI)	P-value
	n (%)	All M/XDR-TB patients				Stratified by XDR-TB	
Resistant to ofloxacin						Excluded from analyses	
Yes	47 (22.3)	1.76 (0.97–3.20)	0.064	1.82 (1.00–3.32)	0.050		
No	163 (77.3)	Reference					
Not known	1 (0.5)						
Resistant to thioamide							
Yes	63 (29.9)	1.65 (0.925–2.95)	0.090	–	–	–	–
No	147 (69.7)	Reference					
Not known	1 (0.5)						
Resistant to all three second-line injectable agent							
Yes	17 (8.1)	2.20 (0.99–4.90)	0.054	2.27 (1.16–5.06)	0.046	2.20 (0.99–4.91)	0.054
No	194 (91.9)	Reference				Reference	
Different resistance groups							
Total number of resistant drugs of tested[2]	5.0 (2-9)	1.35 (1.11–1.64)	0.003	1.35 (1.11–1.64)	0.003	1.28 (1.02–1.61)	0.033
XDR-TB							
XDR-TB	43 (20.4)	2.31 (1.30–4.10)	0.004	–	–	Excluded from analyses	
MDR, non-XDR	168 (76.6)	Reference					
Factors related to treatment							
Duration of treatment in months[2]	18.1 (1.6–53.7)	0.93 (0.90–0.97)	<0.001	–	–	–	–
Was any injectable included into the regimen							
No	29 (13.7)	0.44 (0.23–0.84)	0.013	3.19 (1.37–7.41)	0.007	3.110 (1.33–7.26)	0.009
Yes	182 (86.3)	Reference		Reference		Reference	
SLDs stopped due to side effects							
No	134 (63.5)	0.559 (0.30–1.05)	0.070	–	–	0.38 (0.16–0.90)	0.029
Yes	77 (36.5)	Reference				Reference	

Table 2. *(Continued)*

Characteristic	M/XDR-TB patients	Crude HR (95% CI)	P-value	Adjusted HR[1] (95% CI)	P-value	Adjusted HR[1] (95% CI)	P-value
	n (%)	All M/XDR-TB patients				Stratified by XDR-TB	
Number of drugs given in the intensive phase[2]	6.0 (4–8)	1.17 (0.81–1.71)	0.41	–	–	–	–
Number of drugs given in the continuation phase[2]	4 (0–7)	0.712 (0.62–0.82)	<0.001	0.73 (0.63–0.84)	<0.001	0.75 (0.64–0.87)	<0.001
Fluorquinolone included to the regimen							
No	44 (20.9)	0.726 (0.39–1.34)	0.31	–	–	0.24 (0.06–0.92)	0.037
Yes	167 (79.1)	Reference					
Thioamide included to regimen							
No	41 (19.4)	0.78 (0.41–1.50)	0.46	–	–	–	–
Yes	170 (80.6)	Reference					
Seromycin included to regimen							
No	24 (11.4)	0.53 (0.26–1.58)	0.084	–	–	–	–
Yes	187 (88.6)	Reference					
Aminosalicylic acid included to the regimen							
No	54 (25.6)	1.29 (0.65–2.49)	0.47	0.23 (0.07–0.78)	0.017	0.21 (0.06 – 0.68)	0.010
Yes	157 (74.4)	Reference					
Pyrazinamide included to the regimen							
No	34 (16.1)	0.61 (0.32–1.16)	0.13	–	–	–	–
Yes	177 (83.9)	Reference					
Amoxicillin/clavulanate included to regimen							
No	44 (20.9)	0.71 (0.37–1.33)	0.28	–	–	–	–
Yes	167 (79.1)	Reference					
Clarithromycin included to regimen							
No	184 (87.2)	0.70 (0.33–1,49)	0.35	–	–	–	–
Yes	27 (12.8)	Reference					

[1] Each hazard ratio (HR) has been adjusted for all other characteristics in the respective subset of variables. [2] Values are given in median and range (minimum and maximum). [3] All foreign born persons were from a country of the former Soviet Union. XDR-TB: extensively drug-resistant tuberculosis; MDR-TB: multidrug-resistant tuberculosis; M/XDR-TB: extensively drug-resistant tuberculosis and multidrug-resistant tuberculosis; n: number.

Paper IV

A total of 2,449 patients, 1,777 (72.6%) males and 674 (27.5%) females with newly diagnosed respiratory TB and M/XDR-TB were included in this study (Figure 5). Out of all study subjects 321 (13.1%) were diagnosed with M/XDR-TB, of whom 224 (69.8%) were males and 97 (30.2%) females. A total of 34 cases were diagnosed with XDR-TB. Out of the 2,210 subjects tested for HIV-infection, 131 (5.9%) were positive. The mean age of the males was 44.3 (standard deviation, SD 10.0 years) and that of the included females 42.2 (SD 10.9 years). More than half (54.2%) of the subjects were Estonians, the majority with secondary or lower education (93.1%) and confirmed as having non-MDR-TB (64.6%). During the overall follow-up period, a total of 661 (27.0%) patients died. A total of 2,013 (82.2%) were successfully treated and 182 (7.4%) died during TB treatment, of whom 63.8% were males (95 out of 149) and 63.6% females (21 out of 33) who died from TB. The treatment success among males with non-MDR-TB was 84.3% and among males with MDR-TB 56.3%, whereas the respective figures among females were 86.3% and 68.0%.

The notification rate of new respiratory TB stratified by age groups was higher among males than among females (Figure 12). In both Cohort 1 and Cohort 2 the difference in female mortality from all causes vs. the general female population was larger than the difference in male mortality from all causes vs. the general male population; the SMR was 10.0 and 6.24 among females and 5.3 and 3.46 among males, respectively.

Cohort 1 (males with new respiratory TB)

During the follow-up period, 535 deaths (8,858 person-years; average follow-up time 5.0 years) occurred among 1,775 males diagnosed with new respiratory TB compared to the expected 100.99 (SMR 5.30; 95% CI 4.85–5.75) (Table 3).

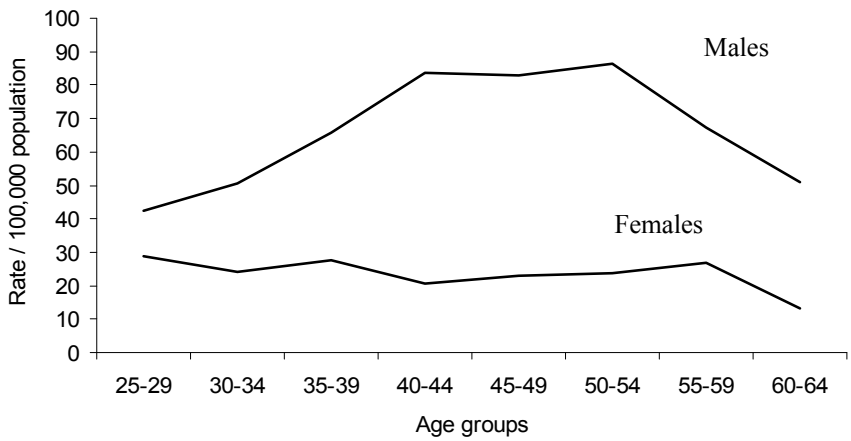

Figure 12. Notification rate among the study IV patients diagnosed with new respiratory tuberculosis in Estonia, 2002–2009.

Table 3. Observed number of deaths and standardized mortality ratio (SMR) with 95% confidence interval (CI) among patients diagnosed with new respiratory tuberculosis (Cohort 1), Estonia, diagnosed during the period 01.01.2002–31.12.2011 (modified from IV)

ICD-10	Cause of death	Males			Females		
		Deaths	SMR	95% CI	Deaths	SMR	95% CI
A00–Y98	All causes	535	5.30	4.85– 5.75	126	10.00	8.25– 11.74
A15–A16	Respiratory tuberculosis	137	147.69	122.96–172.42	29	459.67	307.85–660.16
B20–B24	HIV disease	30	58.24	39.30– 83.14	11	165.78	82.75–296.63
C01–C15, C18–C22, C32, C50	Alcohol-related cancers[1]	19	4.06	2.44– 6.34	6	4.02	1.47– 8.74
C01–C16, C18–C22, C25, C30–C32, C34, C53, C56, C64–C68, C92	Smoking-related cancers[2]	50	3.18	2.36– 4.20	13	5.27	2.81– 9.01
I00–I99	Diseases of the circulatory system	86	2.44	1.95– 3.02	16	4.46	2.55– 7.24
J00–J99	Diseases of the respiratory system	23	5.68	3.60– 8.53	10	30.59	14.67– 56.25
J40–J44	Chronic lower respiratory diseases	5	5.88	1.91– 13.73	3	49.85	10.28–145.68
K00–K93	Diseases of the digestive system	34	4.79	3.32– 6.70	17	16.07	9.36– 25.74
V01–Y98	External causes	104	4.59	3.71– 5.48	13	7.80	4.15– 13.33
F10, I42.6, K70, X45	Selected alcohol-related causes	57	4.85	3.67– 6.28	20	16.28	9.94– 25.14

[1]Among alcohol-related cancers, breast cancer (C50) was applicable only for females. [2] Among smoking-related cancers the cancers of cervix uteri (C53) and ovary (C56) were applicable only for females. ICD-10: International Classification of Diseases and Related Health Problems, version 10.

Table 4. Observed number of deaths and standardized mortality ratio (SMR) with 95% confidence interval (CI) among successfully treated patients with new respiratory tuberculosis (Cohort 2) in Estonia, diagnosed during the period 01.01.2002–31.12.2011 (modified from IV)

ICD-10	Cause of death	Males			Females		
		Deaths	SMR	95% CI	Deaths	SMR	95% CI
A00–Y98	All causes	318	3.46	3.08– 3.84	70	6.24	4.86– 7.88
A15–A16	Respiratory tuberculosis	32	38.50	26.34–54.36	1	17.97	0.45– 00.10
B20–B24	HIV disease	14	30.49	16.67–51.16	4	65.48	17.84–167.66
C01–C15, C18–C22, C32, C50	Alcohol-related cancers[1]	15	3.48	1.95– 5.74	6	4.51	1.66– 9.82
C01–C16, C18–C22, C25, C30–C32, C34, C53, C56, C64–C68, C92	Smoking-related cancers[2]	36	2.49	1.74– 3.44	10	4.56	2.18– 8.38
I00–I99	Diseases of the circulatory system	66	2.04	1.58– 2.60	15	4.70	2.63– 7.75
J00–J99	Diseases of the respiratory system	17	4.63	2.69– 7.41	7	23.98	9.64– 49.41
J40–J44	Chronic lower respiratory diseases	4	5.07	1.38–12.98	2	37.33	4.52– 34.83
K00–K93	Diseases of the digestive system	28	4.36	2.90– 6.30	13	13.82	7.36– 23.63
V01–Y98	External causes	75	3.69	2.90– 4.62	7	4.71	1.89– 9.71
F10, I42.6, K70, X45	Selected alcohol-related causes	40	3.78	2.70– 5.14	16	14.67	8.39– 23.83

[1] Among alcohol-related cancers, breast cancer (C50) was applicable only for females. [2] Among smoking-related cancers the cancers of cervix uteri (C53) and ovary (C56) were applicable only for females. ICD-10: International Classification of Diseases and Related Health Problems, version 10.

A total of 137 men died of respiratory TB. Mortality was increased in all groups of causes of death assessed: due to HIV disease (SMR 58.24; 95% CI 39.30–83.14), external causes of death (SMR 4.59; 95% CI 3.71–5.48), neoplasms, including alcohol-related (SMR 4.06; 95% CI 2.44–6.34) and smoking-related cancers (SMR 3.18; 95% CI 2.36–4.20) and selected alcohol-related causes (SMR 4.85; 95% CI 3.67–6.28). There was also an excess mortality due to the diseases of the respiratory (SMR 5.86; 95% CI 3.60–8.53), digestive (SMR 4.79; 95% CI 3.32–6.70) and circulatory (SMR 2.44; 95% CI 1.95–3.02) systems.

Being diagnosed with MDR-TB increased the relative risk of death due to respiratory TB (ARR 2.98; 95% CI 2.00–4.44). Furthermore, the relative risk of all cause mortality was higher among cases with MDR-TB compared to those with non-MDR-TB (ARR 1.58; 95% CI 1.24–2.02). Older persons, persons of foreign ethnicity or with a lower level of education had a relatively higher risk of all cause mortality and mortality due to respiratory TB.

Cohort 1 (females with new respiratory TB)

A total of 126 deaths (3,806 person-years; average follow-up time 5.6 years) occurred among 674 females diagnosed with new respiratory TB, compared to the expected 12.60 deaths (SMR 10.00; 95% CI 8.25–11.74) (Table 3). A total of 29 females died due to respiratory TB. As with males, there was an increased mortality in all assessed groups of causes of death. The mortality was notably increased due to HIV disease (SMR 165.78; 95% CI 82.75–296.63), but also due to external causes of deaths (SMR 7.80; 95% CI 4.15–13.33), selected alcohol-related causes of death (SMR 16.28; 95% CI 9.94–25.14), neoplasms, including smoking-related cancers (SMR 5.27; 95% CI 2.81–9.01) and alcohol-related cancers (SMR 4.02; 95% CI 1.47–8.74), along with diseases of the respiratory, digestive and circulatory systems (Table 3).

The relative risk of death due to respiratory TB among females increased in cases of MDR-TB compared to those of non-MDR-TB and bacteriologically non-confirmed TB (ARR 3.26; 95% CI 1.42–7.50). The all cause mortality and mortality due to respiratory TB was increased in cases were the subjects were of foreign ethnicity (ARR 1.94; 1.63–2.32 and ARR 2.38; 95% CI 1.69–3.37, respectively) or older than 45 years of age (ARR 1.97; 1.65–2.35 and ARR 2.02; 95% CI 1.42–2.88, respectively). A lower level of education conveyed increased risk of all cause mortality (ARR 1.65; 95% CI 1.3–1.96).

Cohort -2 (successfully treated males)

A total of 318 deaths (7,950 person-years, average follow-up time 5.5 years) occurred among the 1,438 successfully treated males, compared to the expected 92.01 deaths (SMR 3.46; 95% CI 3.08–3.84). A total of 32 deaths occurred due to TB. The excess mortality was observed in all assessed groups of causes of death, although the SMRs were smaller than in Cohort 1 (Table 4).

Across the sub-groups of successfully treated males, having had MDR-TB did not increase the relative risk of all cause mortality as compared to the non-MDR-TB patients. As with Cohort 1, foreign ethnicity (ARR 1.65; 95% CI 1.32–2.07), lower level of education (ARR 1.44; 95% CI 1.15–1.78) and older age (ARR 2.00; 95% CI 1.58–2.53) increased the all cause mortality.

Cohort 2 (successfully treated females)

A total of 70 deaths (3,420 person-years, average follow-up time 6.0 years) occurred among the successfully treated 575 females as compared to the expected 11.22 deaths (SMR 6.24; 95% CI 4.86–7.88). One person died due to respiratory TB. The excess mortality was observed in most of the assessed groups of causes of deaths; however, as among the males, the SMRs were lower than in Cohort 1 (Table 4).

Having successfully treated MDR-TB did not increase the relative risk of all cause mortality compared to the non-MDR-TB patients. Foreign ethnicity (ARR 1.87; 95% CI 1.17–3.01) or older age (ARR 4.03; 95% CI 2.36–6.87) were associated with higher risk of all cause mortality among females.

6. DISCUSSION

The aim of the chapter is to discuss the findings of all four papers as a whole as to answer the main study question, i.e. the impact of M/XDR-TB on the TB notification rate, disease recurrence and mortality, rather than to discuss separately the interlinked specific findings of the four studies.

In Estonia, as elsewhere, M/XDR-TB is a man-made phenomenon (I–IV). Starting in the 1990s the TB incidence began to increase and reached the highest rates in 1998 when the NTP was established. In fact, in Estonia it was not merely a TB epidemic, but rather a combined TB and M/XDR-TB epidemic (I–IV) as is also shown in the studies by Lockman et al. and in WHO reports (13, 93). One of the main barriers to reach the Stop TB targets in the European Region, which Estonia is part of, is the high proportion of difficult-to-treat MDR-TB (I). Historically, the incidence of TB and M/XDR-TB has been influenced by clinical factors along with the socio-economic conditions and HIV infection. Does this still hold true for contemporary Estonia?

6.1. TB and M/XDR-TB incidence (I–IV)

Poverty (II)

In order to assess the association between poverty and TB, we used GDP per capita, available from 1998, as an indicator of deprivation (II). We found that, while the GDP was gradually increasing, the TB and M/XDR-TB incidence decreased, particularly after 2002, when a decade had passed after the sharp economic and political changes occasioned by the break-up of the Soviet Union. However, the association between TB and poverty is complex and social conditions have a strong influence on the spread of TB infection on the one hand and defence mechanisms of the host on the other (1). There is a variety of indexes for grading poverty, each encompassing different factors. In 2005, the GDP per capita has been used to assess deprivation among European Union countries by Fahey et al. (146). In a different paper Fahey (147) outlines the concept of complex and simple relative deprivation. British studies confirmed a strong association between TB and poverty in Liverpool in the 1980's and in metropolitan areas of London in the 1990's by using the Jarman and Townsend simple deprivation indices (148, 149). Based on our current findings, we can conclude that the future of TB epidemics in Estonia depends partly on the economic development of the country.

TB and HIV and M/XDR-TB co-infection (I–IV)

We have currently confirmed that HIV has a major impact on TB and M/XDR-TB epidemics in Estonia (I). This has also been proven for high-HIV prevalence areas, such as Southern and Eastern Africa (2). In 2001, there was an upsurge of TB/HIV co-infection in Estonia (II–IV), which significantly heightened TB

incidence (II). Furthermore, we confirmed an excess mortality due to AIDS among new respiratory TB and M/XDR-TB cases during, as well as after, successful treatment of TB (IV). There is sufficient evidence from other researchers to support the concept of the deadly liaison of TB and HIV in the European region (150). It is known that HIV infection suppresses the cell-mediated immunity contributing to the susceptibility of the co-infected person to TB (48, 151). HIV infection also increases the progression and severity of TB by impairing granuloma formation and recruitment of CD4 lymphocytes into the lungs and elaboration of cytokines by bronchoalveolar immunocompetent cells (48, 151). On the other hand, TB leads to an increase in the viral load in HIV-infected persons by activating innate adaptive signalling cascades that stimulate HIV-1 replication (151). In context with the high mortality rate among HIV-infected patients with XDR-TB, a hypothesis exists that the resistant TB bacteria, often considered to be of a lower relative fitness compared to drug sensitive strains, may still thrive well in the condition of immune suppression (32). In line with this view, since Estonia is one of the countries with the fastest growing HIV epidemics in the world (152), a significant increase in TB and M/XDR-TB incidence ought to occur in the nearest future unless more effort is made to decrease the occurrence and, thus, the co-occurrence of both diseases.

National Tuberculosis Programme and treatment of TB and M/XDR-TB (I–III)

Since 1998, the NTP has been implemented in Estonia to improve the management of TB and M/XDR-TB (II–III). The cornerstones of the NTP are the countrywide access to good quality laboratory services and anti-TB drugs, including SLDs. The NTP is aligning its targets to the Stop TB Strategy announced in 2006, which aims at achieving at least 70% detection and an 85% cure rate (44). The new WHO targets for a treatment success rate by 2015 are even higher: 90% among TB cases and 75% among MDR-TB cases (5). Although the average treatment success for the global 2003 cohort was 82%, in the WHO European Region with high M/XDR-TB prevalence, it was only 75%. Thus, M/XDR-TB turns out to be the main barrier to reaching the target (I). By 2010, the global treatment success among newly-diagnosed TB was already 85%, but only 74% in the WHO European Region (2).

The mean treatment success among all diagnosed pulmonary non-MDR-TB cases in Estonia was 80.8%, or 53.1% among MDR-TB cases but only 47.7% among XDR-TB cases (II). As expected, the treatment success among the selected MDR-TB and XDR-TB patients was higher, being 63.1% and 53.3%, respectively (III). It is estimated that the treatment success among M/XDR-TB cases has to be far above 50% to cut the transmission of infection and, therefore, to decrease the incidence (6). Although currently the number of XDR-TB patients in Estonia is still low, the suboptimal treatment success of these cases is of great concern as the likelihood of continued transmission of the XDR-TB infection in society is high. Not surprisingly, the treatment success among the XDR-TB patients has been reported to be lower than that of MDR-TB worldwide. In a meta-analysis of nine studies, the treatment success of the

XDR-TB cases ranged from 34% to 67% (153), while in a study from South Korea, the treatment success was reported to be as low as 18% (71). In a study from Peru (69) the treatment success of XDR-TB was 60.4% compared to 66.3% among MDR-TB patients. For comparison, in a different study from Estonia (66), the treatment success among XDR-TB cases was 40.7%, close to what we found in our study (II).

We found that the combined treatment success among selected M/XDR-TB patients that were treated with SLDs for longer than one month was 61.1% (III), which is rather similar to the success reported in two recent surveys: 62% (mean 95% CI 57–67) among the 36 reviewed MDR-TB studies by Johnston et al. (62) and 64% (mean 95% CI 59–68%) among the 29 reviewed studies using individualized treatment regimens by Orenstein et al. (64). There are numerous reasons why the treatment success among M/XDR-TB patients is generally low: socio-economic, clinical, and managerial (154). The socio-economic factors have been extensively described in many countries, including in Estonia (115). This Estonian study showed that a history of imprisonment, alcohol abuse, being foreign born, being homeless and jobless and living in an urban area were predictors of poor treatment outcome among patients with pulmonary tuberculosis. The same factors were prominent in case of M/XDR-TB, where these mentioned risk factors are already operative for the development of M/XDR-TB in the first place, as is also shown by Faustini et al. (52). The low treatment success among M/XDR-TB patients in our study could have been influenced in part by the lengthy treatment that lasted more than 20 months (III), which possibly increases the defaulter rate. In our study (III), we concluded that the low treatment success was largely due to the high default rate (22.3%), rather than to the ineffectiveness of the treatment regimens. The ineffectiveness or/and toxicity of the treatment regimens would be presumably expressed by failure and death rates. The pooled proportion of those who died (8.1%) and those who failed (8.5%) in our study was 16.4%, which was less than the percentage of those who defaulted. The risk factors for default among TB and M/XDR-TB patients have been described in various settings in the world (154, 155) including in Estonia (115). Kliiman et al. found that the risk factors for default are largely socio-economic, i.e. urban residence, unemployment, alcohol abuse, and history of previous anti-TB treatment (115).

We demonstrated that the implementation of the NTP in Estonia together with the other factors such as the increase in GDP, contributed to the 7.01% yearly decrease in the incidence of TB and 5.5% of M/XDR-TB (II). It is considered that in developing countries an effective TB programme could achieve 7–10% and exceptionally, even 15% of the yearly decrease in the TB notification rate (6). However, we found no studies assessing the average annual decrease in the M/XDR-TB notification rate globally, and the present study (II) evaluated it for the first time in Estonia. Despite our finding that the M/XDR-TB incidence has decreased annually by 5.5% in Estonia, one might interpret this to be too low to achieve the global targets, especially as HIV infection is still on the rise and the relative fitness and following transmissibility of RMP-

resistant mutant strains of *M. tuberculosis* in the society might not differ from that of drug-sensitive TB (32, 38). However, in case of a possible benign TB epidemic (36, 37), the earlier described treatment success among the non-MDR-TB cases, as well as M/XDR-TB cases, has probably contributed to the observed decrease of the incidence of TB and M/XDR-TB in Estonia (II).

Second-line anti-TB drugs (II, IV)

The availability of SLDs in Estonia accelerated the decrease in incidence of TB, as well as that of M/XDR-TB (II). However, the introduction of the country wide availability of the SLDs after the first centralized procurement in 2001 did not have a significant additional impact on incidence of TB. The reason might be that the SLDs were to some extent available already before the centralized procurement, although not for full-course therapy. On the other hand, although prominent in Estonia, the proportion of M/XDR-TB cases is probably still too low to have a significant impact on the incidence in such a short time. The successful treatment of TB and M/XDR-TB depends, apart from other determinants, also on the effectiveness of the treatment regimens. In our study (III) the older WHO recommendations (141) for treatment of M/XDR-TB were used; therefore, the treatment success might improve if the recommendations of the WHO MDR-TB guidelines published in 2011 (84) are applied. However, it is acknowledged that the currently used SLDs are generally less effective in the treatment of TB than FLDs (3, 6). There are several novel anti-TB drugs in the pipeline (156, 157), such as bedaquiline (158, 159) and delamanid (160). However, limited evidence is available regarding the role of these drugs in M/XDR-TB treatment.

Evidence exists that the side effects of the FLDs (161), particularly in combination with anti-retroviral therapy (162), are contributing to the heightened default rate. Little is known about the exact magnitude of the effect of treatment with SLDs on the adherence to treatment; however, the multiple well-documented side effects of the SLDs (163–168) and the long treatment duration of M/XDR-TB should not be underestimated. The effect of the SLDs on mortality during treatment and later on, after successfully completing the treatment, has not been studied. Currently, we found that among our study subjects (IV) mortality due to the diseases likely to be affected by the SLDs, such as gastrointestinal, hepatic, and cardio-vascular disturbances, cancers, was similarly increased not only among the diagnosed but also successfully treated TB and M/XDR-TB patients. This suggests a modest impact of the SLDs compared to the FLDs on the later mortality.

6.2. TB recurrence and mortality (II–IV)

To measure the long-term effectiveness of the M/XDR-TB treatment regimens, we analysed the TB recurrence and mortality after being diagnosed with MDR-TB and after successful completion of the treatment (III). Among the M/XDR-

TB patients, the cumulative disease-free survival was significantly lower in XDR-TB than in MDR-TB. However, among those patients who were successfully treated, the two cohorts did not differ from each other in terms of TB recurrence and mortality (III). More importantly, we demonstrated that after successful treatment, the risk of death among patients with M/XDR-TB did not increase compared to the patients with drug-sensitive TB (IV). In this light, our findings point out the paramount importance of achieving treatment success, whatever the resistance pattern is. This is also supported by the fact that after successful treatment, the risk factors for all cause mortality had a comparable effect in all three sub-groups, i.e. patients with a history of MDR-TB, non-MDR-TB or bacteriologically non-confirmed TB (IV).

In our study (III) TB recurrence occurred in 8.5% of M/XDR-TB patients over an 8-year follow-up period, which was also the longest follow-up period published so far. Lee et al. demonstrated that in a selected cohort of MDR-TB patients, the 2-year recurrence was 4.4% (10). In our study (III), the 2-year recurrence was even lower (Figure 11), suggesting that the treatment regimens used to treat M/XDR-TB in Estonia are reasonably effective.

Paradoxically, we found that the previous anti-TB treatment had a significant negative impact on the disease recurrence among successfully treated M/XDR-TB patients (III). The previous anti-TB treatment could be associated with possibly larger inflammatory damage of the lung tissue resulting in decreased lung reserve and scarring. This could affect the drug concentration in the affected area and, possibly, even the ability to kill all bacteria. On the other hand, it has also been shown that the retreatment cases are more prone to have boosted behavioural challenges that negatively influence their possible cure (169).

Among all M/XDR-TB patients TB recurrence and later mortality were more likely to occur when the resistance of the pathogen to the anti-TB drugs was more extensive but also when there was a resistance to all three second-line injectable drugs or a resistance to PAS (III). Our current finding of PAS as an important agent in the treatment regimen differs from that in the meta-analysis of 9,153 patients by Ahuja et al. (116), where the use of just fluoroquinolones and thioamides were found to be important to achieve treatment success. Nonetheless, considering that the analysis by Ahuja et al. (116), as well as our study, was not blind, it is difficult to make a definite statement regarding the role of a particular drug. However, one may still conclude that the combination therapy has a prominent role in the treatment of M/XDR-TB. Complimentary to the aforementioned findings, the total number of anti-TB drugs used during the continuation phase of treatment was found to be significantly protective against disease recurrence (III), possibly due to the lower effectiveness of SLDs compared to that of FLDs (6, 170). However, being ill with XDR-TB did not result in a higher TB recurrence as compared to MDR-TB-non-XDR-TB among our study subjects (III). It can be reasoned that in the case of XDR-TB it would still be possible to compose a treatment regimen with an inclusion of an injectable agent of proven susceptibility (3, 84). On the other hand, the more

vulnerable hosts might have died during the treatment course, no matter what is the resistance pattern or the risk factors affecting the TB recurrence and later survival of the successfully treated patients (III, IV). In cases of XDR-TB, adding fluoroquinolone to the regimen, even if the pathogen was resistant to it, was still effective to avoid disease recurrence (III). This finding could be associated with 1) a different level of resistance among the bacterial population (25) in the affected tissue and 2) possible misinterpretation of the DST for SLDs in general and for fluoroquinolones in particular (171, 172). TB was more likely to recur among XDR-TB patients when any of the SLDs were stopped due to their side effects. This is understandable because of extensive resistance and loss of the benefits of combination therapy (18). The median length of treatment among those patients who later developed TB recurrence, as well as among those, who remained TB-free was approximately 20 months (III), which is similar to the finding by Ahuja et al. (116). Nowadays, there is no clear consensus about the duration of M/XDR-TB treatment with the currently available anti-TB drugs. Nine-month chemotherapy for MDR-TB patients has been piloted in Bangladesh with excellent results, 87.9% cure (173). However, the extent of drug-resistance prevailing in that pilot project was considerably lower than that in Estonia (I–IV). Based on our findings (III), we can recommend for treatment of M/XDR-TB in Estonia a ≥20 month combination therapy with a higher rather than with a lower number of second-line drugs in the intensive as well as in the continuation phase.

Smear positivity at the start of treatment (III)

Smear-positivity at the start of TB treatment was proven to be a risk factor for the disease recurrence in both MDR-TB and XDR-TB patients (III). Smear-positivity has been found to be a significant predictor of disease recurrence in drug-susceptible TB without HIV infection (174, 175). Smear-positivity is linked to the severity of disease (176), which in turn may be associated with longer patient and/or health care related delay (177). Early case finding, early diagnosis and early commencement of the SLD treatment need to be enforced to prevent the recurrence of M/XDR-TB.

Sex differences (III, IV)

Along with numerous studies on TB patients (77, 91–93), we currently found that male sex was an independent predictor of the disease recurrence and mortality among the M/XDR-TB patients in Estonia (III). The review by Holmes et al. (178) demonstrated that although in industrialized countries the prevalence of TB infection was almost equal among males and females below 10–16 years of age, the TB prevalence (179) as well as the notification rates (178) were initially higher among females up to 24–34 years of age, but shifted towards increased notification rates among males older than 34 years. In Estonia, the notification rates among new respiratory TB cases in both sexes aged 25 to 64 years (IV) followed the trends similar to those found in low-

income countries, for example in Tanzania during the period 1986–1991 (178). It is acknowledged that there are sex differences in TB, which are partly explained by socio-economic and cultural factors. It has been assumed that in low-income countries, there could be under-reporting among women due to social disparities and unequal access to health care facilities (178). This is apparently not a predominant cause in Estonia nor qualifies the country for a low-income definition by the World Bank. On the other hand, a survey comparing alcohol consumption in Estonia and Finland during the period 1994–2006 found that alcohol consumption among Estonian males is estimated to be three times higher than among females (180). In our present study (IV), the all cause SMR among females was higher than that among males. It is possible that the life-style-associated risk factors for death have a stronger negative impact on females than males. Further studies are needed to compare the risk factors for TB disease and later mortality between males and females in Estonia. Alcohol abuse and tobacco smoking are widely acknowledged risk factors for TB infection, TB disease and mortality (100, 181–183).

While the socio-economic factors have been extensively explored, the role of biological sex differences such as the role of sexual hormones, sex-related genetic background and genetic regulations and metabolism is not clear (184, 185) and necessitates further research.

It is anticipated that when TB incidence falls in Estonia below 30/100,000, the sex-specific TB notification rates will follow those observed during the last 40 years in industrialized countries (178), i.e. higher notification rates among younger females, similar rates in the age group 25–34, followed by relatively higher rates among older males.

Status of foreign birth (III, IV)

Being foreign born increased the risk of TB recurrence and mortality among diagnosed pulmonary M/XDR-TB patients (III) and was a risk factor for all cause and TB-mortality among patients with respiratory TB (IV). It is considered that a period of 2–5 years is crucial for TB occurrence in immigrants (186) and has been attributed to socio-economic disparities in the host country (149). The country of origin is also important: a person born in a high-TB-incidence country is more likely to be infected at the place of origin and has therefore a higher risk of developing TB. Furthermore, Weinstock (187) implies that chronic stress among immigrants has a manifold effect on the health in overall and immune system in particular. In our studies (III, IV) the foreign born persons have lived in Estonia more than 5 years, which may imply that the risk factors which have been operative during the first 2–5 years continue their influence later on in Estonia. Given global trends for migration it can be assumed that the proportion of immigrants will increase in Estonia as the GDP per capita increases in the country. Therefore, there is a need to develop a comprehensive public health policy (188) to address the health needs of this particular population group.

6.3. Causes of death (IV)

The mortality of patients with respiratory TB and particularly that of respiratory M/XDR-TB was hundreds of times higher than that in the general population (IV). Unfortunately, the same was true even after the TB patients had successfully completed their treatment, although the treatment should presumably provide a stable cure. The important finding was that during an average follow-up of more than 4 years (IV), the patients diagnosed with TB and MDR-TB also had an increased risk of all cause mortality in comparison to the general population (IV). In our study (IV), the risk of death following the diagnosis was higher among M/XDR-TB patients compared to the non-MDR-TB patients, which is in-line with the findings of other authors (189).

There are only a few studies assessing SMR among the non-MDR-TB patients. However, we are unaware of country wide studies with as high a proportion of M/XDR-TB patients as has been the case in Estonia. Two studies from India with an average follow-up of 1.6 (92) and 3.3 (128) years, respectively, assessed mortality of DOTS patients and found a 4.2-fold and 6.1-fold increase in all cause mortality, compared to the general population, respectively.

In our study, the all cause mortality remained higher compared to that of the general population even after successful treatment (IV). In a study from Liverpool which involved mainly non-MDR-TB patients an 11-fold excess mortality was found among successfully treated patients, compared to that in the general population (99). In a similar study from Ethiopia, 4.5-fold excess all cause mortality was found among TB cases after successful treatment (91).

In our current study, we found no significant difference for the risk of death among the successfully treated M/XDR-TB compared to the successfully treated non-MDR-TB patients (IV). To our knowledge there are no comparable studies available. Our results may suggest that after successful treatment, the risk factors in TB and MDR-TB sub-groups have a comparable effect on the risk of mortality. Researchers from England (190) have found that after successful completion of TB treatment, the patients acquired a healthier lifestyle (i.e. with less smoking and alcohol consumption), which, although not yet addressed, might also be the case in Estonia.

The excess mortality due to HIV disease among diagnosed, as well as successfully treated respiratory TB patients (IV), was not unexpected given the rapidly growing and decade-long HIV epidemic in Estonia. HIV infection is a well-known major risk factor for developing TB disease (50, 51), but also for death during (77, 100) and after TB treatment (100).

We found increased mortality due to causes affected by smoking, such as neoplasms, diseases of the circulatory system (191), and chronic lower respiratory diseases (192). It has been shown that there is a significant risk of death due to cancer among smokers in Estonia (193). It is well established that smoking (11, 103, 105, 106, 109, 194) and alcohol abuse (100, 111) are determinants of TB disease. Alcohol abuse, but less clearly tobacco smoking are

contributing factors for the poor treatment outcome of TB patients (98, 100, 110, 111, 194). Smoking has been implicated in reducing mucociliary clearance as well as in affecting the length of cilia in the airways (195). This mechanism could possibly also affect the innate defences of the host organism against *M. tuberculosis* (109). Furthermore, tobacco smoke is considered to turn off the production of TNF-α by the macrophages in the lungs, thereby increasing the likelihood of the progression of an infection to TB disease (107, 196). The effect of smoking is well studied in the context of human cancers (138).

In Paper IV, the mortality due to the diseases of the respiratory system, particularly chronic lower respiratory diseases, was significantly increased in comparison with the general population. Currently, tobacco smoke remains the primary risk factor for chronic lower respiratory diseases, including chronic obstructive pulmonary disease (COPD) (197). However, among non-smokers as well, COPD and chronic airflow obstruction is often considered to be a risk factor for PTB (192). On the other hand, PTB is identified as one of the predictors of COPD and chronic bronchitis (11, 192, 198–200). The excess mortality due to smoking-related disease (IV), assuming the interaction between smoking and TB among study subjects, might be the cause of the increased mortality due to the chronic lower respiratory diseases in our study (IV). The possible mechanisms for chronic airflow obstruction after TB are airflow limitation as a consequence of lung scarring and bronchial stenosis. Furthermore, TB increases the activity of matrix metalloproteinases, which contribute to the damage of the alveolar tissue observed in COPD (192, 201, 202). On the other hand, factors like impaired mucociliary clearance and low body mass index affect cell-mediated immunity in COPD and may predispose occurrence of bacterial infections including also TB (192, 203). Nevertheless, the mechanisms discussed are not completely understood, nor is the mechanism of HIV infection as a cause of pulmonary emphysema (204). Further studies are therefore needed to understand the complex interactions between TB, HIV, COPD, and tobacco smoking.

In study IV, we grouped together the main alcohol-related causes of death (205), such as mental and behavioural disorders due to the use of alcohol, alcoholic cardiomyopathy, alcoholic liver disease, and accidental poisoning by alcohol. This was done due to the recognised misclassification of alcohol poisoning in the mortality statistics in Estonia (126). The excess mortality due to these causes was found among the males, but even more among the female subjects in comparison to the general population (IV). This finding and the fact that in our study (IV) only a third were women leads to the possibility that females are particularly vulnerable to life-style factors. The problem of alcohol abuse in Estonia in general (180) and among TB and MDR-TB patients in particular (115) has been identified by several authors. Expectedly, poverty, malnutrition and related diseases are rampant among alcohol abusers (205). Indeed, among the study subjects (IV), the mortality due to alcohol-related cancers (138) had increased. Furthermore, there was an excess mortality of the study subjects compared to that of the general population due to external causes

of death (IV), which are known to be alcohol-related (205, 206). Also, the mortality due to respiratory diseases was increased in our study (IV). As with TB, an increase in mortality from other lower respiratory tract infections, such as pneumonia, has been attributed to alcohol abuse (205). However, the exact extent to which the mortality due to respiratory diseases is attributed to alcohol has yet to be determined.

The findings that both diagnosed and successfully treated TB and MDR-TB patients are at risk of dying from alcohol- and smoking-related causes (IV) highlights the importance of addressing the socio-economic drivers behind smoking and alcohol abuse.

The level of education (IV)

We found that an educational level lower than secondary was associated with a higher risk of mortality (IV). Lower education has been formally associated with both a higher risk of TB (100, 164) and poor treatment outcome (175). In a multinational study from 16 European countries, which included persons aged ≤30 years, subjects with higher levels of education had significantly lower mortality rates (207). In a survey from Lithuania, survival of M/XDR-TB patients was influenced, apart from other factors, by a lower education level (208).

Age (IV)

We found currently that all cause mortality and mortality from TB increased with advancing age (IV). Higher age has been found to be a risk factor for death during anti-TB treatment in the majority of former studies (78, 80, 94–96). In particular, the effect of higher age has been attributed to co-morbidities (100). However in our study it could as well have reflected limited access to health care services among older people in Estonia.

The link between TB, HIV, tobacco smoking and alcohol and substance abuse epidemics is well established (11). Furthermore, smoking, alcohol abuse, educational status, and social marginalization are closely linked to malnutrition and poverty (51), as demonstrated also by the present studies from Estonia (II–IV).

7. CONCLUSIONS

- One of the main barriers to reaching the global targets for TB control in Estonia, as well as internationally, is the high rate of M/XDR-TB. We found that in Estonia the TB and MDR-TB epidemic is closely connected to the HIV epidemic and interlinked with the higher mortality related to the lifestyle factors of tobacco smoking and alcohol abuse, as well as social factors such as educational status, social marginalization and poverty. To improve TB and M/XDR-TB management in general and the M/XDR-TB treatment outcome in particular, the TB-related service package should take into account all the listed challenges.

- From 1998, the TB and M/XDR-TB incidence has decreased in Estonia in a close time relation to launching of the NTP, countrywide availability of the SLDs and growth of the wealth of the population. The increased prevalence of HIV infection during the last decade has fuelled an increase in the incidence of TB, which is anticipated to continue during the forthcoming years. To avoid colliding TB/HIV and even worse, a difficult-to-treat M/XDR-TB and HIV co-epidemic, it is crucial to decrease the TB incidence faster than the current annual decline of 7.07% and 5.5%, respectively.

- An effort should be made by the health care services in Estonia to improve the treatment outcome of M/XDR-TB patients to that of the WHO-recommended 75%. The proportion of successfully treated M/XDR-TB patients within the first GLC-approved project was as low as 61.1%, mainly due to the high proportion of defaulters. Besides decreasing the defaulter rate, we recommend for treatment of M/XDR-TB in Estonia a combination therapy with the duration of ≥20 months and with a higher rather than a lower number of SLDs during the intensive phase, as well as during the continuation phase.

- The M/XDR-TB recurrence in Estonia was 8.5%. Males, persons of foreign ethnicity and those who were previously treated for TB or M/XDR-TB were at high risk for M/XDR-TB recurrence. The risk factors for increased all cause and TB mortality included as well the factors of male sex and foreign ethnicity besides higher age and lower level of education. More attention should be directed to persons of foreign ethnicity, as they are at higher risk of disease recurrence as well as all cause and TB mortality. The trends for international migration suggest that the proportion of foreign immigrants will increase in the forthcoming years, attracted by the increasing national wealth of Estonia. A more comprehensive immigration policy, considering the health issues, including TB, should be developed in Estonia.

8. FUTURE RESEARCH

1. Evaluation of the effectiveness of the treatment of the M/XDR-TB patients with the novel drugs compared to the SLDs used in our studies up to now.

2. For further evaluation of the performance of the NTP, assessment of overall and cause-specific mortality among TB and M/XDR-TB patients in comparison with a population group matched for socio-economic status.

3. Evaluation of the actual problem of alcohol abuse and tobacco smoking among TB and M/XDR-TB patients in relation to 1) the general population and 2) to a population group matched for socio-economic status.

4. Assessment of the quality of the TB-related care provided to the foreign born in comparison to Estonian-born persons.

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SUMMARY IN ESTONIAN

Tuberkuloos Eestis rõhuasetusega ravimresistentsele tuberkuloosile: koguhaigestumus, korduvhaigestumus ja suremus

Tuberkuloos (TB) on nakkushaigus, mille tekitaja on peamiselt õhu kaudu leviv *Mycobacterium tuberculosis*. Peamine nakkusallikas ja nakkuse levitaja on baktereid eritav ehk nn lahtist TB-d põdev inimene. Pärast nakatumist püsib 10%-ne eluaegne risk haigestuda TB-sse (1).

Maailma Terviseorganisatsiooni (MTO) andmetel haigestus 2011. aastal TB-sse 8,7 miljonit ja suri 1,4 miljonit inimest (2). Enamik juhtudest diagnoositi Kagu-Aasias, Vaikse ookeani lääneosas ja Aafrikas (2).

Inimese immuunpuudulikkuse viirus (HIV) on üks peamisi TB-sse haigestumust soodustavaid tegureid. 2011. aastal oli kogu maailmas ligi 13% TB-haigetest HIV-infitseeritud, neist enamik Aafrikas. Samal aastal suri TB-sse 0,99 miljonit inimest ja lisaks veel 0,43 miljonit HIV-koinfitseeritud TB-haiget (2).

Viimastel aastakümnetel on kogu maailmas tõusnud haigestumus ravimresistentsesse TB-sse. Multiresistentne TB (MDR-TB) on TB vorm, mille puhul *M. tuberculosis* pole tundlik kahe kõige efektiivsema TB- ravimi, isoniasiidi ja rifampitsiini suhtes (2). Eeldatakse, et igal aastal haigestub maailmas ligikaudu 630 000 inimest MDR-TB-sse. MDR-TB põhjuseks peetakse ebaregulaarset, ebapiisava annuse ja vale kombinatsiooniga ravimite kasutamist. 2011. aastal oli kokku 27 riiki, kus MDR-TB-haigete osakaal kõikide TB-haigete seas ületas 6%, kahjuks oli Eesti üks neist (2). Lisaks MDR-TB-le on levimas nn eriti resistentne TB vorm (XDR-TB), mille puhul on haigustekitaja *M. tuberculosis* resistentne lisaks isoniasiidile ja rifampitsiinile veel vähemalt ühele fluorokinoloonile ja vähemalt ühele teise rea süstitavale TB-ravimile (3). 2011. aasta lõpuks teatasid 84 riiki, nende seas Eesti, XDR-TB haigusjuhtude esinemisest. Eeldatakse, et ligikaudu 9% kõikidest MDR-TB-haigetest põevad XDR-TB-d, mis võrdub ligikaudu 58 500 haigusjuhuga (4).

MTO eesmargiks maailmas on saavutada aastaks 2015 uute haigete ravi efektiivsus 90% ja MDR-TB juhtude ravi efektiivsus 75% (5). See eeldab õigeaegset TB ja M/XDR-TB diagnoosimist ning kohest efektiivset ravi. Ravi efekti hinnatakse nii vahetult ravikuuri lõpus kui pikemas perspektiivis, mille puhul on haiguse taaspuhkemine üks olulisem näitaja. Maailmas oli 2010. aastal ravi alustanud uute haigete ravi efektiivsus 87%, kusjuures Aafrikas, kus on suur HIV-infitseeritud TB-haigete osakaal, oli see 82%. Seevastu Euroopas, kus MDR-TB-haigete osakaal on maailma suurim, oli ravi efektiivsus vaid 67% (2). Multiresistentsete haigusvormide ravitulemus on ravimite madalama efektiivsuse, tugevate kõrvaltoimete ja pikema ravikestuse tõttu halvem võrreldes ravimtundliku TB-ga (3). Nii oli MDR-TB-haigete ravi efektiivsus maailmas 48%, kuid XDR-TB-haigetel ainult (33%) (2).

2008. aastal avaldatud süstemaatiline ülevaade järgi retsidiveerub haigus ravimtundlike haigete puhul 0–14% juhtudest (8). HIV-infitseeritud TB-haigetel esineb TB retsidiive sagedamini kui mitteinfitseeritute seas (8,2 vs 2,2/100

inimaasta kohta) (9). MDR-TB retsidiveerumist käsitlevaid uuringuid on aga tehtud vähe. Lõuna-Koreas ravitud haigetel esines näiteks kaheaastase jälgimisaja jooksul retsidiive 4,4%-l patsientidest, kes kasutasid individualiseeritud raviskeeme (10).

On teada, et TB, HIV-nakkus, suitsetamine ja alkoholi kuritarvitamine on kujunenud epideemiateks ning omavahel tihedalt seotuna (11) nad tõstavad TB-sse haigestumise ja surmariski.

Eestis hakkas TB- ja MDR-TB-haigestumus kasvama 1993. aastal, pärast Nõukogude Liidu lagunemist, mis ulatuslike sotsiaalsete ja majanduslike muutuste näol tõi kaasa nn üleminekušoki. Eestis 1994. aastal läbi viidud esimene ravimiresistentsuse uuring tuvastas MDR-TB 10,3%-l uutest TB juhtudest (13). 1998. aastal jõudis TB-haigestumus Eestis haripunkti – 59,4 uut juhtu/100 000. Samal aastal, võitlemaks kasvava TB ja M/XDR-TB ohuga, kehtestati Eestis Riiklik TB-tõrje programm, mis juhindus MTO otseselt kontrollitava ravistrateegia (DOTS) printsiipidest: 1) valitsuse toetus TB-tõrje programmile; 2) prioriteet TB-juhtude passiivsele (haige pöördumisel) ja riskirühmades aktiivsele avastamisele; 3) standarditud 6–8-kuulise otseselt kontrollitava ravi skeemide kasutamine; 4) kõigi vajalike TB-ravimitega varustamise tagamine; 5) ühtne registreerimis- ja kontrollsüsteem. Seoses kõrge MDR-TB-sse haigestumuse ja kallite reservpreparaatide puudumisega taotles Eesti ühena esimesest viiest riigist MTO ja Peatage TB Partnerluse (Stop TB Partnership) MDR-TB komitee (GLC) luba järgida tollal uudset MDR-TB käsitlust ning võimalust osta hea kvaliteediga reservpreparaate alandatud hindadega. Üks käesoleva uuringu eesmärkidest oli hinnata eelpool mainitud esimese MDR-TB projekti ravi efektiivsust.

Eestis ja kogu maailmas varitseb oht, et kahe samaaegselt laieneva ja teineteist õhutava epideemia, M/XDR-TB ja HIV koosmõju tulemusena väljub TB- ja M/XDR-TB-epideemia kontrolli alt. Pärast üle 10 aastat kestnud TB-programmi on oluline analüüsida TB-sse ja M/XDR-TB-sse haigestumust ja suremust ning neid mõjutavaid tegureid, et tõhustada TB-vastast tööd ning pakkuda tulemusrikkamat patsientide ravi.

UURINGUTE EESMÄRGID

Uuringute üldine eesmärk oli hinnata TB ja M/XDR-TB mõju TB haigestumusele, korduvhaigestumusele ja suremusele ning määratleda surma põhjused TB ja M/XDR-TB-haigetel.

Töö alaeesmärgid olid:

Töö osa I Määratleda kitsaskohad ülemaailmses TB-tõrjes jõudmaks rahvusvaheliselt seatud eesmärkideni globaalsel tasandil.

Töö osa II Hinnata üleriigilise TB käsitluse ja reservpreparaatide kasutuse efekti kopsu-TB ja spetsiifiliselt kopsu-MDR-TB haigestumusele arvestades Eesti majandusnäitajate mõju ning HIV-infektsiooni ja TB koosesinemist.

Töö osa III Hinnata esimese MTO MDR-TB komitee projekti (GLC) raames ravitud MDR-TB- and XDR-TB-haigete ravi efektiivsust ning hinnata korduvhaigestumise riskitegureid Eestis.

Töö osa IV Hinnata ravimtundlikku TB-d ja MDR-TB-d põdevate patsientide üld- ja põhjusomast suremust võrreldes seda Eesti kogurahvastiku omaga nii pärast diagnoosimist kui ka pärast edukat ravi.

PATSIENDID JA MEETODIKA

Töö osa I võttis kokku erialakirjanduse andmed leidmaks kitsaskohti ülemaailmse TB-tõrje tarvis.

Töö osa II hindas TB ja MDR-TB haigestumust ning sisemajanduse koguprodukti, reservrea preparaatide ja HIV-nakkuse olemasolu efekti haigestumisele Eestis. Sellesse uuringusse (II) kaasati kõik ajavahemikus 01.01.1998–31.12.2006 diagnoositud kopsu-TB esmased haiged ja retsidiivid.

M/XDR-TB-haigete ravi efektiivsuse hindamiseks (III) kaasati uuringusse esimese MTO MDR-TB komitee projekti raames ravitud MDR-TB- ja XDR-TB-haiged, kes olid diagnoositud nimetatud TB vormidega ajavahemikus 1.08.2001–31.07.2003. Uuringust arvati välja haiged, keda oli teise rea TB-ravimitega ravitud alla ühe kuu. Korduvravijuhtude esinemise hindamiseks moodustati kaks haigete rühma: 1) kohort 1, kuhu hõlmati kõik diagnoositud haiged ja 2) kohort 2, kuhu kuulusid ainult edukalt ravitud haiged.

Hindamaks TB ja MDR-TB patsientide üld- ja põhjusomast suremust võrreldes kogurahvastikuga (IV), kaasati uuringusse kõik esmaselt hingamiselundite TB-sse haigestunud patsiendid ajavahemikus 01.01.2002–31.12.2009. Haigete suremust ravi jooksul ja samuti pärast edukat ravi hinnati eraldi kohordis 1 ja kohordis 2.

Andmekogumine ja statistiline andmetöötlus

Uuringu andmebaas põhines Eesti Tuberkuloosi Registri ning Tartu ja Tallinna tuberkuloosi ja mükobakterioosi laborite andmebaasidel (II–IV). Andmed aasta keskmise rahvaarvu kohta saadi Eesti Vabariigi Statistikaametist; andmed HIV-infitseerituse kohta Tervise Arengu Instituudist ning andmed surmade kohta Eesti surmaregistrist rahvusvahelise haiguste ja nendega seotud tervise-

probleemide statistilise klassifikatsiooni 10. versiooni (RHK-10) järgi. Andmed sisemajanduse koguprodukti kohta saadi Eurostatist.

Andmete statistiliseks analüüsiks (II, III) kasutati tarkvarapaketi SPSS®, versiooni 17.0; töö osa IV puhul kasutati tarkvara Visual FoxPro 6.0 ja Stata 10. Analüüsiti vaid täielike andmetega haigusjuhte.

Trendi hindamiseks kasutati Cochrani-Armitage`i trendifunktsiooni ja lineaarset regressioonanalüüsi analüüsimaks TB-vastaste reservpreparaatide, HIV-infektsiooni ning sisemajanduse koguprodukti efekti TB ja M/XDR-TB haigestumusele.

Elulemust ja korduvhaigestumust analüüsiti Kaplani-Meieri meetodiga, kusjuures rühmadevahelise erinevuse testimiseks kasutati Breslow'i testi. Riskitegurite hindamiseks (III) kasutati Cox'i regressioonanalüüsi meetodit Wald'i statistiliste kriteeriumitega.

Standarditud suremusmäär (SMR) arvutati eraldi meestele ja naistele, selle korral jagati tegelik surmajuhtude arv eeldatava surmajuhtude arvuga. Eeldatav surmajuhtude arv arvutati korrutades soo- ja vanuse järgi esitatud inimaastad vastavate Eesti rahvastiku suremuskordajatega. Eraldi analüüsiti suremust TB tagajärjel ja suremust muudel põhjustel kahe perioodi kohta: 2002–2006 ja 2007–2011. SMR-idele arvutati 95% usaldusvahemik (95% CI) eeldades Poisson'i jaotust. Mitmemõõtmelist Poisson'i regressiooni mudelit kasutati hindamaks vanuse, hariduse, rahvuse ja MDR-TB efekti suremusele.

UURINGUTE PEAMISED TULEMUSED

Töö osa I

2003. aastaks oli ülemaailmne TB ravi edukus 82%, mis oli lähedal globaalsele eesmärgile 85%. Siiski, Aafrikas oli see vaid 72% ja Euroopas 75%. Peamised kitsaskohad TB-vastases võitluses rahvusvaheliselt seatud eesmärkideni jõudmisel oli kõrge MDR-TB-haigestumus Euroopas ja kõrge HIV-infektsiooni haigestumus Aafrikas (130). 2004. aastal kuulus Eesti kümne kõige kõrgema MDR-TB haigestumusega riigi hulka maailmas, s.o riikide hulka, kus MDR-TB-levimus on üle 6,5% kõikidest TB juhtudest. Konkreetselt oli Eestis MDR-TB-haigestumus esmaste TB-haigete seas 12,2%. Lisaks Eestile kuulusid esikümnesse veel: Kasahstan (14,2%), Tomski oblast Vene Föderatsioonis (13,7%), Karakalpakstan Usbekistanis (13,2%), Leedu (9,4%) ja Läti (9,3%) (130, 145).

Detsembriks 2006 oli käivitunud 53 GLC egiidi all olevat projekti MDR-TB käsitluseks 42 riigis. Tänu GLC projektidele said riigid võimaluse osta soodustusega hea kvaliteediga reservrea preparaate MDR-TB-haigete raviks. Eesti oli üks esimesest viiest GLC egiidi all tegutsevast MDR-TB-projektist, esimese 84 MDR-TB-haige ravi efektiivsus oli 51.2% (43/84). Viie esimese MTO MDR-TB-projekti (Eesti, Läti, Peruu, Filipiinid ja Tomsk Vene Föderatsioonis) raviedukus koondarvestuses oli 77% esmajuhtude ja 69% korduvravijuhtude puhul (61).

Töö osa II

Uuringusse kaasati 5196 esmast kopsu-TB juhtu ja retsidiivi, kellest 4086 (71,7%) olid mehed. Patsientide vanuse mediaan oli 45,9 aastat. HIV-infitseerituse andmed olid teada 3033 isikul (58,4%), neist 132 (4,4%) olid HIV-positiivsed. Ravimtundlikkus oli määratud 3862 isikul (74,3%), kellest omakorda 760 (19,7%) põdesid MDR-TB-d. Viimastest omakorda 95-l (17,1%) oli XDR-TB.

Ajavahemikul 1998–2006 vähenes TB-haigestumus 50,2-lt juhult kuni 32,7-ni 100 000 inimese kohta. TB-tõrje programmi käivitumise järgsel 1998. aastal vähenes haigestumus keskmise kiirusega 3,3 juhtu 100 000 inimese kohta aastas (langus keskmiselt 7,02% aastas, P=0,007). Sama perioodi jooksul kahanes M/XDR-TB haigestumus vastavalt 6,7-lt 3,5-le. Keskmine aastane haigestumise langus oli seega 1,7 juhtu 100 000 inimese kohta aastas ehk 5,5% aastas (P=0,008).

Vaatlusperioodi ajal suurenenud sisemajanduse koguprodukt mõjutas TB ja M/XDR-TB-haigestumuse langust (vastavalt P<0,001 ja P<0,001). TB-vastaste reservpreparaatide olemasolu alates 2002. aastast kiirendas haigestumuse langust. Samas tõusis HIV-infitseeritute TB-haigete osakaal, mis mõjutas TB haigestumust olulisel määral negatiivselt (vastavalt P<0,001 ja P=0,001). Ajavahemikul 1998–2006 uuringusse kaasatud mitte-MDR-TB-haigete ravi efektiivsus tõusis 72,7%-lt 77,4%-le (P=0.009), kuid MDR-TB-haigetel ravi efektiivsus seevastu alanes 54,8%-lt 51,1%-le (P=0,018). XDR-TB-haigete ravi koondtulemus oli 47,7%, kuid vähese arvu uuritavate tõttu polnud võimalik ajatrendi statistiliselt hinnata.

Töö osa III

Uuringus osales 211 ajavahemikul 01.08.2001–31.07.2003 diagnoositud MDR-TB-haiget, sealhulgas 43 XDR-TB-haiget. Haigete jälgimine kestis kuni 31.12.2010 või kuni järgmise haiguse episoodi alguse, surma või lahkumiseni Eestist. Keskmine vanus oli 42,9 aastat. Uuritavatest 154 (73,0%) olid mehed ja 172 (81,5%) eestlased. Kokku 197 haiget (93,4%) olid testitud HIV-nakkuse suhtes ja neist 5 (2,5%) olid HIV-positiivsed.

Edukas ravitulemus saavutati kokku 129 (61,1%) haige puhul, MDR-TB-haigete puhul oli ravi efektiivsus 63,1% ja XDR-TB-haigete puhul 53,5%. Edukalt ravitud haigete ravikestus jäi 6,1 ja 53,7 kuu vahele, keskmine ravikestus oli 19,8 kuud. Edukalt ravitutest 11 isikut (8,5%) haigestus uuringu jooksul TB-sse teistkordselt. Kokku 47 isikut (22,3%) katkestas ravi, 18 (8,5%) osutusid ebaedukalt ravituteks ja 17 (8,1%) surid.

Kõiki haigeid arvesse võttes oli keskmine jälgimisaeg 98,1 kuud, mille jooksul 38 haiget (18,0%) suri TB-sse. Kumulatiivne haigusvaba aeg oli pikem MDR-TB-haigetel võrreldes XDR-TB-haigetega. Taashaigestumist esilekutsuvad riskitegurid olid: meessugu, mitte-eesti rahvus, eelnevalt põetud TB, ravi alustamisel TB-bakterite suhtes positiivse röga äige olemasolu, ravimresistentsus suurema hulga ravimite suhtes, resistentsus kahe reservrea aminoglükosiidi

või tsüklilise peptiidi suhtes ning eelnimetatud preparaatide ja lisaks streptomütsiini puudumine raviskeemist. Suurema tõenäosuse selleks, et haigus ei retsidiveeruks, andis para-aminosalitsüülhappe lisamine raviskeemi ja suurema arvu ravimite kasutamine järelravifaasis. XDR-TB-haigete puhul olid riskitegurid samad, ent lisaks oli retsidiveerumise vältimiseks oluline ofloksatsiini lisamine raviskeemi ja ravimite mitteärajätmine kõrvaltoimete tõttu.

Edukalt ravitud 129 haigest ei erinenud M/XDR-TB- ja mitte-MDR-TB-haiged omavahel haiguse retsidiveerumise tõenäosuse poolest. Ainsaks teguriks, mis mõjutas TB kordumist edukalt ravitute puhul, oli TB põdemine enne uuringu algust.

Töö osa IV

Ajavahemikul 01.01.2002–31.12.2011 kaasati uuringusse 2449 esmast hingamiselundite TB-i põdevat haiget vanuses 25–64 aastat, neist 1777 (72,5%) olid mehed ja 674 (27,5%) naised. HIV-infektsiooni suhtes oli testitud 2210 isikut (90,2%), kellest 131 (5,9%) olid HIV-positiivsed. Keskmine vanus oli meestel 44,3 aastat (standardhälve (SD) 10,0 aastat) ja naistel 42,2 aastat (SD 10,9 aastat). Rohkem kui pool haigetest (54,2%) olid eestlased. Enamik (93,1%) olid kesk- ja madalama haridusega ning põdesid mitte-M/XDR-TB-i (64,4%). Kokku 2013 haiget (82,2%) osutusid edukalt ravituteks, kuid samas 182 (7,4%) surid TB-ravi ajal. Haigete jälgimine kestis kuni 31. detsembrini 2011 või kuni järgmise haigusepisoodi alguse, surma või lahkumiseni Eestist. Kogu uurimisperioodi jooksul suri 661 haiget (27,0% uuringusse kaasatutest). Diagnoositud 1775 mehest suri 535 (8858 inimaastat; keskmine jälgimisaeg 5,0 aastat), SMR oli 5,3 (95% CI 4,85–5,75) ja diagnoositud 674 naisest suri 126 (3806 inimaastat; keskmine jälgimisaeg 5,6 aastat), SMR oli 10,00 (95% CI 8,25–11,74). TB tõttu suri 137 meest ja 29 naist.

Nii meestel kui naistel olid surmapõhjused nii pärast diagnoosimist kui ka pärast edukat ravi sarnased. Kõrge oli suremus HIV-nakkuse tõttu. Tähelepanuväärne oli kõrge suitsetamisest ja alkoholi kuritarvitamisest tingitud surmade osakaal võrreldes kogurahvastikuga, seda nii pärast TB-sse haigestumist kui ka pärast eduka TB-ravi lõppu. Meeste puhul olid täiendavad riskitegurid mitte-eesti rahvus, madalam haridus, kõrgem iga ja M/XDR-TB esinemine. Pärast edukat ravi ei erinenud MDR-TB-haiged suremuse poolest mitte-MDR-TB-haigetest. Naiste puhul olid surma riskitegurid samad, mis meestel, välja arvatud haridus, mis naistel ei osutunud surma riskiteguriteks.

JÄRELDUSED

– M/XDR-TB on peamiseks takistuseks jõudmaks TB-vastases võitluses nii Eestis kui globaalsel tasandil rahvusvaheliselt seatud eesmärkideni. Antud töö põhjal järeldame, et Eestis on TB ja M/XDR-TB kõrge haigestumus tihedalt seotud HIV-infektsiooniga. TB- ja M/XDR-TB-haigete kõrgem suremus Eestis on mõjutatud sellistest teguritest nagu suitsetamine ja

alkoholi liigtarvitamine, madalam haridustase ja sotsiaalne tõrjutus, mis omakorda on seotud vaesusega. Selleks, et Eestis parandada M/XDR-TB ravi edukust ja tõhustada TB ja M/XDR-TB tõrjet üldisemalt, peavad TB-ga seotud raviteenused olema suunatud kõikide eelmainitud kitsaskohtade vastu.

- Alates 1998. aastast, samaaegselt Eesti Tuberkuloositõrje programmi kehtestamisega ja käsikäes üleriigilise M/XDR-TB raviks vajalike reservrea preparaatide olemasoluga ning sisemajanduse koguprodukt suurenemisega, on TB ja M/XDR-TB haigestumus Eestis vähenenud. Samas on HIV-infitseeritus viimase kümnendi jooksul tõusnud ja eelduste kohaselt jätkab tõusu veel mõne aja jooksul. Vältimaks kahe epideemia, HIV ja TB, eriti aga HIV ja M/XDR-TB koosmõju, on oluline senisest kiiremas tempos alandada TB- ja M/XDR-TB-haigestumust, mis praegu alaneb vastavalt 7,07% ja 5,5% aastas.

- Senisest suuremat tähelepanu on vaja osutada M/XDR-TB-juhtude varasele diagnoosimisele ja samas parandada ravitulemusi, et saavutada MTO poolt soovitatud 75%-ne ravi efektiivsus. Esimese GLC soovituste kohaselt ravitud M/XDR-TB-haigete ravi edukus oli vaid 61,1%, nii madal oli see peamiselt ravikatkestajate tõttu. Meie uurimistööle tuginedes soovitame lisaks ravikatkestuste vähendamisele kasutada Eestis M/XDR-TB-haigete puhul kombinatsioonravi pigem suurema kui väiksema arvu TB-ravimitega. Ravi on soovitatav jätkata vähemalt 20 kuud.

- M/XDR-TB-korduvhaigestumus oli Eestis 8,5%. Meestel, mitte-eestlastel ja eelnevalt TB-d põdenutel on suurem tõenäosus korduvalt haigestuda M/XDR-TB-sse. Samas on TB- ja M/XDR-TB-haigete kogusuremuse ja TB-tingitud surma risk suurem meestel ja mitte-eestlastel nagu ka madalama haridustasemega ja vanematel isikutel. Rohkem tähelepanu tuleb osutada mitte-eestlastest TB-d põdevatele isikutele, sest neil esines rohkem korduvhaigestumist. Samuti oli mitte-eestlastest TB-d ja M/XDR-TB-d põdevatel isikutel võrreldes kogurahvastikuga kõrgem nii kogusuremuse risk kui ka TB-st tingitud surmarisk. Jälgides rahvusvahelisi rändetrende saab oletada, et seoses sisemajanduse koguprodukti suurenemisega võib mitte-eestlastest isikute osakaal lähiaastatel suureneda. Vajalik on välja töötada Eestis terviklik, ka immigrantide tervise ja TB-ga tegelev programm.

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