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Highly drug-resistant tuberculosis in Estonia: Risk factors and predictors of poor treatment outcome

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CONTENTS

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

I. Kliiman K, Altraja A. Predictors of Extensively Drug-Resistant Pulmonary Tuberculosis. Ann Intern Med 2009; 150: 766–775.

II. Kliiman K, Altraja A. Predictors of poor treatment outcome in multi- and extensively drug-resistant pulmonary TB. Eur Respir J 2009; 33: 1085–1094.

III. Kliiman K, Altraja A. Predictors and mortality associated with treatment default in pulmonary tuberculosis. Int J Tuberc Lung Dis Accepted for publication on October 28, 2009.

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ABBREVATIONS

AFB	Acid-fast bacilli
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
DOTS	Directly Observed Treatment, Short-Course
DST	Drug susceptibility testing
HR	Hazard ratio
HIV	Human immunodeficiency virus
IQR	Interquartile range
MDR	Multidrug-resistant
NTP	National Tuberculosis Programme
OR	Odds ratio
SU	Soviet Union
TB	Tuberculosis
WHO	World Health Organization
XDR	Extensively drug-resistant

1. INTRODUCTION

Tuberculosis (TB) is a major global public health problem, which, according to the latest World Health Organization (WHO) estimates, killed about 1.76 million people in 2007 [1]. In 2007, approximately 9.27 million new TB cases occurred and an estimated global TB incidence rate was 139 cases per 100,000 population. Most of the estimated TB cases occurred in Asia (55%) and Africa (31%) and 15% of all estimated incident cases (1.37 million) were human immunodeficiency virus (HIV) positive. Of these HIV-positive TB cases, 79% lived in Africa and 11% in South-East Asia.

TB treatment requires administration of multiple antibiotics over 6 months or more to effect cure but no novel and better drugs have been developed for many years. In addition, during the last decades, highly drug-resistant strains of *Mycobacterium tuberculosis* have emerged to present a serious public health problem. Multidrug-resistant TB (MDR-TB), defined as TB caused by *M. tuberculosis* resistant *in vitro* to isoniazid and rifampicin, the two most powerful first-line anti-TB drugs, came into the global view already in early 1990s and is now widely reported. To date, WHO estimates at least 500,000 new MDR-TB cases annually. Treatment of MDR-TB requires the use of second-line TB drugs, which are less effective, more toxic, and significantly costlier than the first-line drug-based regimens [2]. As a consequence, the treatment success rates of MDR-TB are substantially lower as are the mortality rates notably higher than those of drug-sensitive TB [3].

Since 2006, even worse treatment outcomes and higher death rates have been demonstrated in extensively drug-resistant TB (XDR-TB) [4–9], defined as TB caused by *M. tuberculosis* resistant to isoniazid and rifampicin (i.e. MDR-TB) but additionally resistant to any of the anti-TB fluoroquinolones and at least one of the three injectable anti-TB drugs (capreomycin, kanamycin, or amikacin) [10]. Rising combination of XDR-TB with HIV infection has resulted in even worse outcomes [11–13]. A report of XDR-TB outbreak in South Africa, in a rural area in KwaZulu Natal [11], where 98.1% of the XDR-TB patients (52/53) died with the median survival of 16 days from the time of diagnosis, provided a worrying new evidence of extremely serious consequences of highly drug-resistant TB in a resource-limited area. Of the 53 cases, 44 were tested for HIV and all appeared to be HIV-positive. This landmark finding suggested that XDR-TB with combination of HIV infection can be almost incurable [4,11] and because of the very limited response of XDR-TB to the available drugs, mortality rates among XDR-TB patients are similar to those of the TB patients in the pre-antibiotic era. In the United States, the average cost of treatment for one XDR-TB patient is estimated to reach 483,000 US$, which is approximately twice as much as the treatment cost for one MDR-TB case and more than 30 times higher than the treatment cost for one non-MDR-TB case [14]. XDR-TB has now being reported in more than 50 countries in all regions of the world [15] and WHO estimates emergence of about 40,000 XDR-TB cases worldwide every year. Not only the highest XDR-

TB rates are coming up in countries of the former Soviet Union (SU) and China, but XDR-TB is also being detected in industrialized countries, where TB control has functioned effectively for many years [16–18]. In the United States of America, from 2002 to 2007, 18 XDR-TB cases were diagnosed and the proportion of XDR-TB among MDR-TB was 3.0% [19]. In 2000, Estonia was identified as one of the MDR-TB "hot spots" and has afterwards consistently had one of the highest proportion of MDR-TB and XDR-TB in the world [19,20].

Drug-resistant strains of *M. tuberculosis* develop as a result of mismanagement of susceptible TB. The mismanagement may include inappropriate treatment regimens (e.g., a wrong choice of drugs, dosage, and duration of treatment), programme factors (e.g., irregular drug supply, incompetent health personnel), and patient factors (e.g. poor adherence, mal-absorption). In fact, it could be said that the occurrence of MDR-TB and XDR-TB itself is an evidence of systematic failure of the community to tackle a curable disease [12]. Surveillance data on TB provided by WHO and partners show that both prevention of MDR-TB (through improving basic TB control) and rapid diagnosis and effective treatment of MDR-TB cases (reducing transmission in the community of drug-resistant strains) are necessary to reduce the MDR-TB and XDR-TB rates in the countries with high MDR-TB prevalence.

To achieve the Stop TB Partnership target, which is to eliminate TB as a public health problem, i.e. to decrease the global TB incidence down to a level of less than 1 case per million population by the year 2050, it is important to reach the outcome targets first set in 1991 by the WHO World Health Assembly: to detect at least 70% of the new smear-positive TB cases and successfully treat 85% of them [21]. In 2005, the world-wide TB treatment success rate was 84.7% for new and 71.0% for re-treatment smear-positive cases [22]. The most important preventable cause of poor TB treatment outcome has been found treatment default, which strongly contributes to prolonged infectiousness, high relapse rate, TB-related death, and most importantly, generation of drug resistance [23].

Preventing the development of drug-resistant TB through optimal implementation of WHO-recommended Directly Observed Treatment Short-Course (DOTS) strategy should continue to be the top priority for all countries. Additionally, with improvement of infection control measures to prevent transmission, expansion of high-quality diagnostic services for timely detection, and expansion of involvement of the community to improve patients' adherence, it is possible to prevent further emergence of highly drug-resistant TB.

2. REVIEW OF THE LITERATURE

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

The development of drug-resistant *M. tuberculosis* strains is predicated upon two ways, which both generate artificial selective power on the bacteria: 1) prescription of inadequate non-standard regimens, inappropriate supply of the drugs, or unsupervised drug administration on behalf of the clinicians and 2) inappropriate or irregular intake of the prescribed medications on behalf of the patients [24]. Under selective pressure caused by inadequate (mainly insufficient) regimens or monotherapy, genetic mutants, being naturally resistant to the given antibiotic, emerge to replace the original strain, thus turning an initially drug-susceptible disease to a mono-resistant one. Subsequent cycles generate poly-resistant strains, including MDR-TB. The risks of mutations that cause drug resistance in *M. tuberculosis* have already been defined in most anti-TB medicines. Many of the mutations are point mutations located at known chromosomal regions of *M. tuberculosis* [25]. Hence, drug-resistant strains may arise in previously treated non-drug-resistant patients (acquired drug resistance) or may occur in treatment-naive patients, when the resistant strains are transmitted to infect them (primary drug resistance). Previous inadequate therapy of MDR-TB with second-line drugs, especially an improper use of fluoroquinolones and injectable drugs, either in weak treatment regimens, for inappropriately short duration, or both, might have a major role in the development of XDR-TB strains [26].

MDR-TB was defined in the 1990-s as TB caused by *M. tuberculosis* resistant *in vitro* to at least rifampicin and isoniazid, the two most significant drugs employed in the modern anti-TB regimens. The term XDR-TB was first developed by the US Centers for Disease Control and Prevention (CDC) in March 2005 [27]. XDR-TB was introduced into the public realm at the 36th Conference of the International Union Against Tuberculosis and Lung Diseases (IUATLD) in Paris, France, in October 2005 [28]. 6 months later, in March 2006, the original definition of XDR-TB was published in CDC's Morbidity and Mortality weekly report [16]. At that time, XDR-TB was characterized as a disease caused by *M. tuberculosis* resistant to at least isoniazid and rifampicin among the first-line TB drugs and to at least three of the six main classes of second-line drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and para-aminosalicylic acid). As the initial definition was dependent on difficult-to-perform drug susceptibility testing (DST) and some forms of drug-resistant TB are less treatable then others, the definition of XDR-TB was eventually revised in October, 2006 during the first meeting of the WHO Global XDR-TB Task Force. The definition, which continues to be accepted, requires resistance of *M. tuberculosis* to at least isoniazid and rifampizin, to any fluoroquinolone, and to at least one of the three injectable second-line anti-TB drugs (amikacin, capreomycin, or kanamycin) [10,29].

2.2. Epidemiology of drug-resistant TB

2.2.1. Global epidemiology of drug-resistant TB

According to WHO's "Anti-tuberculosis drug resistance in the world: Report No. 4" [19], it is estimated that 489,139 [95% confidence interval (CI), 455,093–614,215] MDR-TB cases emerged worldwide in 2006, and the global proportion of resistance among all cases was 4.8% (95%CI, 4.6–6.0). Among the newly diagnosed TB cases, the total number of MDR-TB cases was 285,718 (95%CI, 256,072–399,224) resulting in the proportion of 3.1% (95%CI, 2.9–4.3). Among the previously treated cases, the respective data were 203,230 (95%CI 172,935–242,177) and 19.0% (95%CI 18.2–21.3). Since MDR-TB patients usually require treatment for 2 years or longer, the figures of global MDR-TB prevalence may be three times greater than its incidence [30], suggesting that the true number of MDR-TB cases in the world would range from 1,000,000 to 1,500,000. China, India, and the Russian Federation are estimated to incorporate the highest number of the MDR-TB cases. China and India account for approximately 50% of the global MDR-TB burden [19] and 8% and 5% of all TB cases in these countries, respectively, are estimated to have MDR-TB and are thus unlikely to respond to the treatment they currently receive. In the countries of Eastern Europe, on average, 1 out of 5 TB cases has MDR-TB.

By the end of March 2009, XDR-TB had been observed in all continents and a total of 55 countries have reported at least one XDR-TB case [15]. WHO estimates that around 40,000 XDR-TB cases emerge worldwide every year. XDR-TB is a significant problem in the countries of the former SU, where approximately 10% of all MDR-TB cases have been reported to have XDR, ranging from 4% in Armenia to almost 24% in Estonia [19]. Nevertheless, also industrialized countries like Japan have shown a high proportion of XDR-TB among MDR-TB cases. Of the 60 MDR-TB cases, detected from 2002 to 2007 in Japan, 17 (30.9%) were XDR-TB cases [19]. Nevertheless, according to the theory, XDR-TB is anticipated in countries, where second-line anti-TB drugs are widely and inappropriately used.

2.2.2 Epidemiology of drug-resistant TB in Estonia

After collapse of the SU, Estonia experienced substantial political, economic and societal changes associated with declines in many health indicators and resurgence of TB [31]. The incidence of TB, defined as the number of all detected new TB cases per 100,000 population, started to increase in Estonia in early 1990s and doubled after five years of increase in 1997, when 51 new TB cases were diagnosed per 100,000 population. Since 2000, Estonia started countywide implementation of the WHO-recommended DOTS strategy and as a result of the efficient work of the National Tuberculosis Programme (NTP), the TB notification rate, defined as the number of all recorded TB cases per

100,000 population, in Estonia has decreased from 55.0 (in 2000) to 34.7 (in 2007) TB cases per 100,000 [32] (Figure 1).

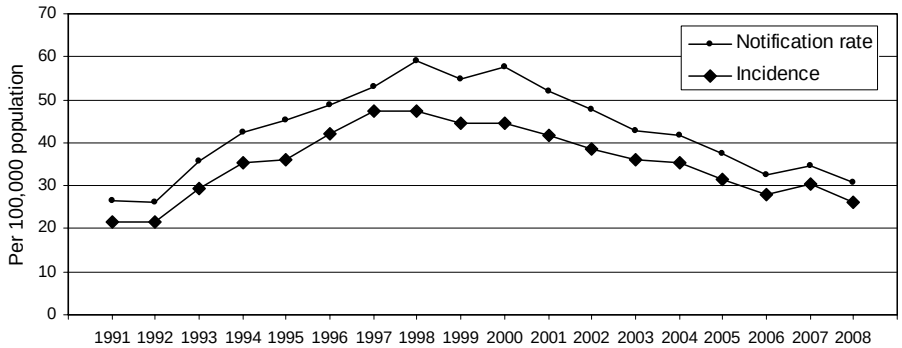

Figure 1. Tuberculosis (TB) incidence (the number of all detected new TB cases per 100,000 population) and notification rate (the number of all recorded TB cases per 100,000 population) in Estonia in 1991–2008. (Data source: National Tuberculosis Registry).

In 2000, Estonia was identified as one of the MDR-TB "hot spots" in the world because of having consistently one of the world's highest proportion of MDR-TB and XDR-TB [19,20]. In August 2001, Estonia started the WHO-recommended DOTS-Plus project for treatment of MDR-TB patients. Since 2000, the TB notification rate decreased 8% per year and is now showing a flat trend in proportions of MDR-TB among new cases, however, the proportions of MDR-TB and XDR-TB have remained still high (Table 1) [19]. In 2005, MDR-TB accounted for 14.1% of all tested new and 48.1% of previously treated cases, whereas 20.6% of all MDR-TB cases represented XDR-TB (11.9% of new and 34.6% of previously treated MDR-TB cases, respectively) [33] (Figure 2). The strains of W-Beijing genotype, known to be associated internationally with large outbreaks of TB and increased virulence [34–37], are predominantly related to MDR-TB in Estonia [38,39] and have substantially contributed to the emergence of drug-resistant TB all over the country.

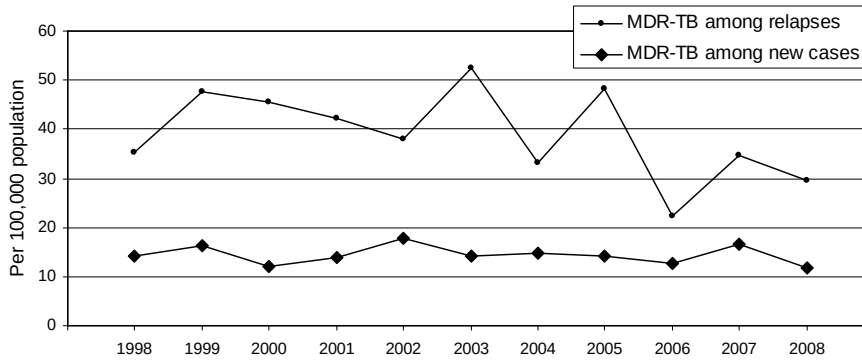

Figure 2. Proportion of multidrug-resistant tuberculosis (MDR-TB) among all cases of tuberculosis with drug susceptibility testing (DST) data in Estonia, 1998–2008. (Data source: National Tuberculosis Registry).

Table 1. Notified tuberculosis (TB) cases in Estonia, 2001–2008. (Data source: National TB Registry)[a].

	2001	2002	2003	2004	2005	2006	2007	2008
All TB cases	708	648	579	561	501	438	467	415
New cases	570	525	490	478	424	373	408	354
	(80.5)	(81.0)	(84.6)	(85.2)	(84.6)	(85.2)	(87.4)	(85.3)
Relapses	138	123	89	83	77	65	59	61
	(19.5)	(19.0)	(15.4)	(14.8)	(15.4)	(14.8)	(12.6)	(14.7)
Of them, MDR-TB cases	98	100	83	70	68	47	69	60
	(13.8)	(15.4)	(14.3)	(12.5)	(13.6)	(10.7)	(14.8)	(14.5)
New cases	53	64	51	51	42	36	52	42
	(54.1)	(64.0)	(61.4)	(72.9)	(61.8)	(76.6)	(75.4)	(70.0)
Relapses	45	36	32	19	26	11	17	18
	(45.9)	(36.0)	(38.6)	(27.1)	(38.2)	(23.4)	(24.6)	(30.0)
Of them, XDR-TB cases	15	11	23	11	14	5	8	6
	(15.3)	(11.0)	(27.7)	(15.7)	(20.6)	(10.6)	(11.6)	(10.0)
New cases	6	5	8	5	5	3	5	4
	(40.0)	(45.5)	(34.8)	(45.5)	(35.7)	(60.0)	(62.5)	(66.7)
Relapses	9	6	15	6	9	2	3	2
	(60.0)	(54.5)	(46.9)	(54.5)	(64.3)	(40.0)	(37.5)	(33.3)

[a] Data are presented as n (%).
MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

The prevalence of HIV infection in Estonia is rising. In 1999, only 12 HIV cases were diagnosed and the overall number of HIV-positive cases was 64. In contrast, during 2008, already 545 new HIV cases were detected and the total number of HIV-positive people reached 6909 by the end of the year 2008 (Data

source: The Estonian Health Protection Inspectorate). In 2005, the estimated adult national HIV prevalence was 1.3% (range, 0.6–4.3%) [40] and in 2008, 9.4% of all TB cases were HIV-infected (Figure 3) (Data source: National TB Registry).

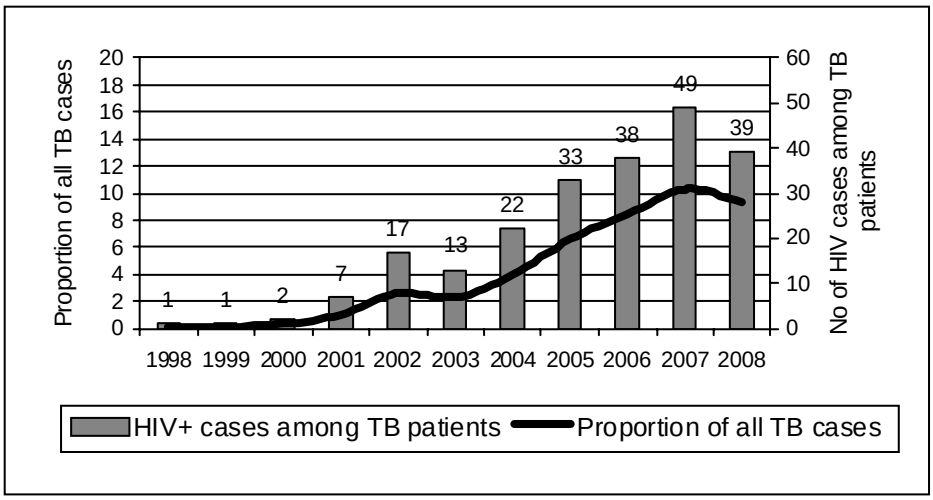

Figure 3. Human immunodeficiency virus (HIV)-infected tuberculosis (TB) cases notified in Estonia and proportion of all TB cases, 1998–2008. (Data source: National TB Registry).

2.3. Treatment of highly drug-resistant TB

General principles for designing a regimen for treatment of highly drug-resistant TB are: 1) use of at least four drugs, whose effectiveness is certain or highly likely, 2) avoidance of drugs for which resistance crosses over, 3) elimination of drugs that are not safe for the patient, 4) inclusion of drugs from the following groups: a) first-line anti-TB drugs, b) injectable anti-TB agents, c) fluoroquinolones, d) oral bacteriostatic second-line anti-TB drugs, and d) anti-TB agents with unclear efficacy in a hierarchical order based on potency, and 5) preparedness to prevent, monitor, and manage adverse effects for each of the drugs selected [25]. There are two options for treatment of MDR-TB and XDR-TB [41]. Standardized combinations of second-line drugs are recommended, but this choice requires representative DST data on specific treatment categories. An alternative approach is to design a regimen on the basis of the individual's history of previous anti-TB therapy and eventually re-tailor it on the basis of the individual DST results. This approach requires a high degree of laboratory capacity necessary to perform DST on most second-line drugs and is time-consuming and laborious for the personnel involved in treatment of TB as well.

The DOTS strategy, consisting of five key elements: 1) governmental commitment, 2) case detection trough bacteriologic evaluation, 3) standardized treatment with supervision and patient support, 4) regular, uninterrupted supply of all essential anti-TB drugs, and 5) a reporting and recording system that allows assessment of treatment, has greatly contributed to improved global TB control over the last 10 years [42,43]. In the high MDR-TB prevalence settings, standardized short-course chemotherapy with first-line drugs and supervised treatment did not provide acceptable success rates [44]. As a result, in 1999, WHO and partners developed a strategy for treatment of MDR-TB, initially termed as "DOTS-Plus" [2,45], which added some new key element to the five tenets of the DOTS strategy. These include: 1) diagnosing based on culture and DST, 2) treatment with second- as well as first-line drugs, and 3) recording and reporting of treatment outcomes. According to the WHO recommendation, the treatment regimens for MDR-TB should contain a minimum of four (and, in some cases, as many as eight) anti-TB drugs at their highest recommended doses during eighteen to twenty-four months [45]. First results from the DOTS-Plus pilot projects indicate that the majority of MDR-TB cases are treatable and well-designed regimens, largely based on second-line anti-TB drugs, can considerably improve the cure rates [25,46]. A recent meta-analysis by Orenstein *et al*. [47], which involved 34 clinical reports with a mean of 250 MDR-TB patients *per* report, acknowledged that the proportion of successfully treated patients increased 1) if the treatment duration was at least 18 months and 2) if the patients received directly observed therapy throughout the course of treatment. Studies that combined both factors had significantly higher success proportions and individualized treatment regimens had slightly higher treatment success than standardized ones, although this difference was not significant.

2.4. Risk factors for drug-resistance in TB

2.4.1 Risk factors for MDR-TB

Previous TB treatment has been widely recognized as a predictor of MDR-TB in the majority of the earlier reports originating from different parts of the world [48–53]. A reported history of previous TB treatment suggests that MDR-TB was acquired during a previous treatment episode. Such an acquired drug-resistance may indicate a failure of TB control efforts due to inadequate case management, interruptions in drug supply, or inadequate drug regimens. In a study by Espinal *et al.* [54], the likelihood of MDR-TB increased progressively along with the length of the previous treatment period. Indeed, the longer is the treatment, the more likely is it's becoming non-standard or interrupted and thus, the higher is the probability of generating strains resistant to the selected drugs. The particular role of treatment interruption has been addressed in previous studies showing that the chance of developing MDR-TB increases among previous TB treatment defaulters [55].

A clear association between MDR-TB and age under 65 years has been pointed out in Europe [56]. In more detail, in a study from Spain [53], an association with MDR and age group 45–64 years was found, whereas in South Korea, MDR-TB was significantly linked to the age under 45 years [52]. Rifampicin, one of the most effective anti-TB agents, was introduced in 1967 and these results thus reflect the era during which rifampicin was already widely used [57].

The issue of gender in association of developing MDR-TB is also intriguing. It has been demonstrated that MDR-TB patients in Western Europe were more likely male. It has been hypothesized that women are more compliant with treatment and therefore less likely to receive inadequate treatment. In contrast, in some reports from the former SU, where the risk of transmission of drug-resistant TB is greater because of wider spread of the MDR-TB infection, female gender was found to be a predictor of MDR-TB [58–62]. Certain predictors of MDR-TB, such as previous TB treatment, are globally ubiquitous in nature. On the other hand, several predictors could have divergent impact in different settings and thus, such risk factors should be always interpreted in context with the local background.

Recently, an association between MDR-TB and HIV infection has been investigated extensively. Most studies from North America have demonstrated a positive association between HIV infection and MDR-TB, which is contrasting to the studies from Africa, where not a single study demonstrated such a relationship [63]. Nevertheless, an association between HIV and MDR-TB has been shown in studies from the former SU, particularly from Donetsk Oblast in Ukraine and Latvia [19]. The results of numerous studies indicate that primary, but not acquired MDR-TB, is associated with HIV infection [64–67]. The reasons why drug-resistant TB is linked to HIV are multiple. The first one is acquisition of rifampicin resistance among HIV-infected patients under treatment for TB. Malabsorption of certain anti-TB drugs, especially that of rifampicin and ethambutol, has been documented in settings, where HIV prevalence is high [19]. This suggests that HIV-positive TB patients may be at greater risk of acquiring resistance due to their decreased bioavailability of the respective drugs, which, in terms of the performance of the drugs, equals to the effect of intermittent therapy. The second group of reasons is related to so-called common exposures. HIV-positive patients and drug-resistant TB patients may share similar risk factors like a history of hospitalization, an intravenous drug abuse, previous imprisonment, socioeconomic distress, and alcohol abuse [13,19,63]. Thirdly, an observed association could be set up by time window. HIV-negative patients are likely to reactivate a latent TB infection acquired for decades ago, whereas HIV-infected patients are likely to reactivate a TB infection acquired more recently by the community-acquired or institutional transmission to a rapidly progressing disease [63].

In prior reports [50–52,68,69], MDR-TB cases were much more likely to have a smear-positive cavitary pulmonary disease, when compared to the non-MDR-TB patients. This phenomenon, most probably related to prolonged

patient delay, can contribute to the spread of drug-resistant strains. Furthermore, MDR-TB has been found to be associated with socially disadvantaged patients, such as homeless population [70], unemployed people [55], intravenous drug users [48,50], and alcohol abusers [53,71,72].

Accordingly to the data from the United States [51,73,74] and Europe [56,75,76], drug-resistant TB has been significantly associated with immigration. This relationship is stronger in recent immigrants than among those, who had lived in the United States for more than 5 years [49], implying that the MDR-TB infection was largely linked to the patient's country of origin. A study by Falzon *et al.* [77] found that within the European Union, TB patients from the former SU countries have the highest frequency of both primary and acquired multidrug-resistance. Immigrants from the former SU have also been identified to be at increased risk of MDR-TB in California, USA, between 1994 and 2003 [51].

Overcrowding in prisons and inability to isolate the resistant cases due to the lack of isolation facilities clearly increase the transmission of resistant *M. tuberculosis* strains. This fact is internationally well documented and an association of MDR-TB either with being a prisoner or with having a history of previous incarceration has been observed in numerous studies [50,55,56,78–80]. In one study [48], a known TB contact and an employment as a health care worker have been demonstrated as independent predictors of multidrug-resistance.

2.4.2. Risk factors for XDR-TB

In contrast to the data regarding MDR-TB, there is little research information available on the predictors of XDR-TB. According to the first published study on XDR-TB risk factors from South Korea, which included 26 re-treatment XDR-TB cases, the presence of bilateral cavities at the time of the diagnosis of MDR-TB [5] and the cumulative duration of previous treatment of 18–34 months were significantly associated with XDR-TB [81]. In a descriptive analysis from the United States [82], which included all TB cases reported from 1993 to 2007, compared with those with MDR-TB, patients with XDR-TB were more likely to have disseminated TB, were less likely to convert to a negative sputum culture, and were longer infectious (median time to culture conversion 183 days in XDR-TB vs. 93 days in MDR-non-XDR-TB). In an analysis, which included all XDR-TB cases diagnosed in Pulido Valento Hospital, Portugal, between April 1999 to June 2007 (n = 69) [83], TB-HIV-co-infection and increased average duration of previous treatments were significant predictors of XDR.

2.5. Risk factors of poor treatment outcome and treatment default

In 2005, the worldwide treatment success rate was 84.7% among the new smear-positive TB cases registered under DOTS and 71.0% among the re-treatment cases [22]. The default rates in these cohorts were 5.4% and 12.0%, respectively. Poor TB treatment outcome and high treatment default rate comprise an increasing threat to public health and TB control due to uncontrolled spread of TB infection and drug resistance, as well as increase in TB relapses and TB-related deaths [84,85]. To take the control, determining predictors of poor treatment outcome and treatment default, especially among those factors, which can be influenced by the people or by the societies, is of supreme importance.

2.5.1. Treatment outcomes of MDR-TB and XDR-TB

Classical MDR-TB cases are treatable, but as attested by previous studies, the treatment of MDR-TB requires use of second-line drugs, which are less effective, more toxic, and costlier than the first-line drug-based regimens [2]. As a consequence, the treatment success rates in MDR-TB cases are substantially lower than those of drug-sensitive TB cases [3,44,86]. In Latvia, where MDR-TB was reported in 14% of newly diagnosed TB patients and in 54% of re-treatment cases in 1996 and where the DOTS-Plus project was commenced in 1998 using an individualized treatment approach, the treatment success rate was 66% among all civilian pulmonary MDR-TB patients who started treatment in 2000 [46]. In a recent report from Tomsk, Russia [87], the success rate of DOTS-Plus project involving both civilian and penitentiary patients was as high as 77%. These studies show that in the conditions of TB programmes, a successful outcome is achievable in at least two-thirds of MDR-TB patients, even in regions of widespread drug resistance. According to the WHO Global Tuberculosis Control 2009 report [88], the highest MDR-TB success rates have been attained in Philippines (73%) and Latvia (71%), followed by the United States (61%). On the contrary, the outcomes were especially poor in Romania (38%) and Morocco (25%).

Since 2006, significantly worse treatment outcomes and higher death rates have been demonstrated in XDR-TB [4,5,89], especially when a combination with HIV infection has been the case [11]. With the currently available drugs, XDR-TB patients are principally left with few, if any, treatment options. According to more recent studies, the XDR-TB treatment success rates in countries with low HIV prevalence ranges from less than 20% in South Korea [90] through 40% in joint data from Estonia, Germany, Italy, and Russian Federation [91] to just over 60% in Peru [92]. In Peru, with an aggressive, comprehensive management programme, 60.4% of the HIV-negative XDR-TB cases and 66.3 % of the MDR-TB cases cured and the risk of death among the XDR-TB

patients did not differ significantly from that among the MDR-TB patients (p = 0.36). The basic principles of management of highly drug-resistant TB in Peru were aggressive drug regimens, use of surgery, frequent contact with the health care worker, and bacteriological assessment. Recent reports [26,93–95] suggest, that management of XDR-TB is feasible within the existing treatment strategies for MDR–TB, but it is necessary to reduce the delay of diagnosis and initiation of appropriate treatment, to use aggressive medical and surgical treatments, and to find means to minimize the transmission if the treatment fails.

In 2005, the treatment success rate of non-MDR-TB in Estonia was 83.6%, but that of MDR-TB was as low as 55.7% [33,96]. Moreover, the proportion of treatment defaulters in Estonia has been exceptionally high, being 10.7% of the non-MDR-TB cases and 21.5% of the MDR-TB cases in 2005. Of all notified MDR-TB cases in Estonia (new and re-treatment cases together) from 2001 to 2006 (n = 466), 56.7% cured or completed the treatment (Estonian TB Registry, unpublished data). Of the 79 XDR-TB patients from the same cohort, only 41.3% reached a successful treatment outcome, i.e. were cured or completed the treatment. The default rates among the MDR-TB and XDR-TB cases were 16.3% and 20.0%, respectively.

2.5.2. Risk factors associated with poor treatment outcome

2.5.2.1. Risk factors associated with poor treatment outcome in MDR-TB

It has been widely recognized that HIV infection significantly reduces the treatment success in MDR-TB and causes a rapid progression of TB to death in both outbreaks and treatment cohorts [11]. More than 50% of HIV-infected MDR-TB patients in Peru died within two months of the diagnosis [97]. Studies with longer follow-up periods observed death rates ranging between 72–89% during 7–16 months of TB treatment [98]. A study from the United Kingdom estimated that immunocompromised MDR-TB patients were nine times more likely to die than those without an immunosuppression [99]. HIV-co-infected MDR-TB patients appear to benefit from antiretroviral treatment against HIV, however, simultaneous management of the treatment of both diseases is complicated. Although the combination of TB treatment and antiretroviral therapy can increase survival in HIV-TB co-infected patients in general, it is less likely to do so in patients with drug-resistant TB [100,101]. In addition, despite antiretroviral therapy reduces the incidence of active TB in HIV-infected people [102], the patients still have a more than five-fold increased risk of developing TB compared to the individuals without HIV infection.

The majority of relevant studies have demonstrated that previous treatment with second-line drugs is significantly associated with poor treatment outcome in MDR-TB [46,59,90]. Also, treatment of MDR-TB with five drugs or less for 3 months or longer has appeared to be a risk factor of poor treatment outcome

[46]. Although the concept of XDR-TB as a poor prognostic factor was introduced only recently [16], resistance to ofloxacin among patients with MDR-TB has been regarded as an independent risk factor for unfavorable treatment outcome already in several reports [46,103]. Expectedly, a treatment regimen containing ofloxacin has been found to be a predictor of successful treatment outcome [104]. In a study involving 240 MDR-TB cases from Italy, Germany, Estonia, and Russian Federation [105], it was found that out of the second-line injectable drugs, resistance to particularly capreomycin, but not to either kanamycin or amikacin, significantly increased the risk of death and treatment failure in MDR-TB and XDR-TB. Nevertheless, the importance of the injectable drugs other than capreomycin cannot be neglected, as in a recent South Korean report, it was found that susceptibility to kanamycin was even better predictor of favorable treatment outcome in MDR-TB than was susceptibility to fluoroquinolones [81]. Based on case reports, linezolid, an oxazolidinone agent, appears to be a promising option for treating MDR-TB and XDR-TB patients [106–108].

An association between gender and treatment outcome has been inconsistent in previous studies. Female gender was found as predictor of poor treatment outcome in a report from Georgia [59] and from Estonia [58]. On the contrary, female gender was associated with treatment success according to an analysis performed in Turkey [109]. Several patient-related factors like a history of intravenous drug abuse [59], consumption of excessive alcohol [87], homelessness [70], and underlying co-morbidity [5] were found to be associated with multidrug-resistance. Body mass index less than 18.5 as a marker of poor nutritional status in patients with TB at treatment initiation has been described as a risk factor of poor treatment outcome in numerous studies [46,94,110]. Patients with more advanced TB with a presence of cavitary or bilateral disease appeared to be at higher risk of poor treatment outcome [58,87], whereas a negative sputum smear result at start of treatment has been inversely related to poor treatment outcome [94].

Former studies indicate, that surgery performed in time increases the probability of favorable treatment outcome [94,109,111–114]. Surgical intervention done before the mycobacterial counts begin to rise should be an option for those with high-grade resistance, relatively localized disease, lack of initial response to non-surgical therapy, and for those who can tolerate the surgery [111,115]. The rationale for lung surgery is removal of the cavitary lesions or areas of destroyed lung that harbor a high burden of *M. tuberculosis*, especially if a highly drug-resistant strain is the case. The patients will be more likely to tolerate surgery if diagnosed and referred early in the course of TB [26]. Surgery as an adjunctive treatment for TB has been performed for 4.3% of MDR-TB patients in South Korea [110], 14.6% of patients with XDR-TB in Peru, and 14.4% of patients with XDR-TB [92] and 63.4% of patients with MDR-TB in the United States [111]. Furthermore, according to a Latvian report [46], 9.3% of the MDR-TB patients underwent surgical interventions leading to a suc-

cessful outcome in 84% of these patients. This result is in line with the findings from other studies from different countries [111].

2.5.2.2. Risk factors associated with poor treatment outcome in XDR-TB

Patients with XDR-TB have significantly heightened risk for death or treatment failure compared to those with MDR-TB having resistance to all first-line drugs and even higher risk compared to those MDR-TB patients in whom susceptibility to at least one first-line drug is still preserved [91]. These data support the observation that the loss of the first-line drugs other than rifampicin and isoniazid significantly worsens the prognosis in MDR-TB cases. Resistance to fluoroquinolones, a key XDR-defining variable, remarkably contributes to increased risk of death and treatment failure [103]. To date, only a few studies have analyzed the risk factors associated with poor treatment outcome in XDR-TB. According to a recent South Korean report, previous TB treatment with second-line drugs and a cavitary disease have appeared to be the risk factors for poor treatment outcome in XDR-TB [90]. In the same study, the use of linezolid and surgical resection were significantly associated with favorable outcome.

2.5.3. Treatment default rate and timing of default

Defaulting rates from standard long-course TB treatment (a historical pre-DOTS-treatment) were between 50% and 82% [116,117]. After starting DOTS implementation, the formerly high default rates decreased and reached to range from 21% in Uzbekistan [118] and 17% in India [119] to 11% in Africa [117] and 9% in Russia [120]. The average worldwide proportion of defaulters in the 2005 cohort was 5.4% among the smear-positive new cases and 12.0% among the re-treatment cases [22]. In MDR-TB patients, the reported default rates are higher ranging from 13% in Latvia [46] to 41% in South Korea [110]. Among the XDR-TB patients in South Korea, 28% interrupted their TB treatment, most of the initial defaulters defaulted again, and only 1.8% of previous defaulters completed the treatment [110] pointing out the issue of a previous default as a risk factor for consequent treatment default.

With regard to the timing of default from TB treatment, it has been found that the majority of defaulters interrupt their treatment during the continuation phase, i.e. during the period following the 2-month intensive phase of the treatment [121]. Most of the defaulting is known to occur during the third and the fourth month of treatment [116,117]. Two studies addressing the risk factors for default particularly among MDR-TB patients [122,123] found similarly that most patients defaulted after having received treatment for at least 6 months. This may be so because at that particular time point, the patients usually feel better and acquire a false impression of being completely cured.

In a study from Hong Kong, among the defaulters with pulmonary TB, 39% were still culture-positive at the time of default [124]. With regard to particularly MDR-TB patients, analogous results have been reported concluding that more than one third of the defaulters were sputum culture-positive at the time of their default and were therefore potentially infectious [122].

2.5.4. Causes of treatment default

The reasons for defaulting from TB treatment are poorly understood. In an Ethiopian study from 1994 [116], the top two reasons for default included social problems and feeling of improvement. In an Ethiopian study [117] published 8 years later, the reasons behind defaulting were distance of more than 10 kilometers from health care institutions (16%), side effects of the medication (14%), and the lack of knowledge about the duration of treatment (16%). In a study from Uzbekistan [118], the two most common reasons for default according to the patients' records were refusal from further treatment (27%) and violation of hospital rules (18%) strongly associated with alcohol abuse. Other frequently recorded reasons were migration (16%) and side effects of the anti-TB drugs (10%).

Two studies, one from South Africa [125] and another from Vietnam [126], have focused on the reasons for initial default. Initial defaulters were defined as patients detected as having bacteriologically confirmed TB who drop out before initiating TB treatment. In both studies, the most frequently reported reason for not starting treatment was directly linked to TB services, in 56% and 80% of the cases, respectively. In the Vietnamese study, 15% of patients did not start TB treatment because they were not aware of their being ill with particularly TB or because they felt well and thought that there is no need for TB treatment.

2.5.5. Risk factors associated with treatment default

In a systematic review of patients' adherence to TB treatment by Munro *et al*. [127], eight primary themes affecting patients' adherence were identified: 1) organization of treatment and care for TB patients, 2) interpretation of illness and wellness, 3) financial burden of TB treatment, 4) knowledge, attitudes, and beliefs about TB treatment, 5) law and immigration, 6) personal characteristics and adherence behavior, 7) treatment side effects and adherence, and 8) family, community, and household influences. A meta-analysis conducted by Brasil *et al*. [128] involving a total of 41 studies found that default from TB treatment was most robustly predicted by difficulties in access to health services and patient training or support for adherence. It was assumed that with treatment adherence training, it is possible to reduce the default rate by about 50%.

Based on earlier studies, the TB-related risk factors for treatment default are diverse. They include a history of previous TB treatment [119], a history of

previous default [124,129,130], and multiple drug resistance [124]. Side effects of anti-TB medication [117,129] have been pointed out as risk factors for default also in numerous studies. Hence, one could suggest that routine screening and aggressive management of adverse events might reduce their negative impact on patients' ability to complete the treatment.

Most predictors for TB treatment default are not primarily connected to TB itself, but have been related to individual patient characteristics, such as male gender [116,119,124,131], poor initial adherence [129], current smoking [129], previous history of incarceration [130,132], unemployment and homelessness [118,133], low educational level [116], abuse of alcohol [118–120,133], or use of any illicit substance [119,120,134,135]. These data suggest that with inclusion of concomitant treatment of substance and/or alcohol addiction, it might be possible to improve TB treatment results.

The data on the smear status at the start of TB treatment as a risk factor for default have remained inconclusive. Sputum smear-positivity at the start of treatment appeared to be a risk factor of treatment default in a study by Jakubowiak *et al.* [133]. However, Hasker *et al.* [118] failed to confirm this and showed on the contrary that smear-positivity is a significant protective factor against treatment default. An explanation is that a smear-negative pulmonary disease is often over-diagnosed as TB and the patients with such a misdiagnosis will hence not benefit from TB treatment and are therefore less likely to complete the respective treatment. Other factors also described as predictors of treatment default include HIV infection [130,136,137], passive case detection (defined as detection of TB after the patient contacted medical care because of his/her symptoms) [119], negative attitude toward the TB care centre [116], a history of concomitant liver disease or lung cancer [124], and particular comorbid conditions, which make the patients more sensitive to the side effects of anti-TB drugs [120]. Earlier studies have demonstrated that better patients' knowledge about the duration of TB treatment [117,138] and better patients' overall knowledge about TB [116] exert a significant protective effect against treatment default. Similar protective effect has been demonstrated with using directly observed treatment in Thailand [139] and with application of social support in Russia [133]. Also, prior reports described a protective effect of family support against treatment default [117,130,140]. In particular, it is meant that the family support can alleviate patient's economic and social problems and provide encouragement.

Two studies have addressed the risk factors for treatment default particularly in MDR-TB patients. A study from South Africa [123] demonstrated that the strongest predictors for default were smoking of marijuana or mandrax during the treatment, having an unsatisfactory opinion about the attitude of health care workers, and indicators associated with low or unstable socioeconomic status. In a study from Peru [122], use of illicit substances, substandard housing conditions, shorter MDR-TB treatment period, and certain health districts were recognized as risk factors for default. To date, there are no studies focusing

particularly on the risk factors for treatment default in XDR-TB patients (English-language MEDLINE search in October 2009).

2.5.6. Survival after treatment default and predictors of mortality

The data on survival after treatment default, as well as on the predictors of mortality after default are very scarce. Only one study from Peru conducted by Franke *et al.* [122], which included only MDR-TB patients, estimated the proportion of deaths among defaulters and identified the risk factors for death after treatment default. Of the traced defaulters, 53% died thereafter with median time to death after treatment default being 273 days [interquartile range (IQR), 103–503 days]. In multivariate analysis, poor bacteriologic response, duration of treatment for less than 1 year according to an individualized regimen, psychiatric disorder, and a high school education were statistically significantly associated with death after default. In a study by Holtz *et al.* [123] involving MDR-TB patients from South Africa, the percentage of defaulters who died thereafter was lower (27%), but the predictors of mortality were not reported. In an analysis from South Africa [141], where MDR-TB patients starting treatment during 1992–2002 were involved, 20% of defaulters died during a 2-year follow-up period. Similar proportion of deaths (22%) has been described among initial defaulters in an Indian report [142].

In contrast to the limited data about the predictors of death after treatment default, several studies have identified the risk factors for death during TB treatment. The majority of studies have demonstrated that MDR-TB [58,85,143–147], XDR-TB [82,110], and HIV infection [148–151] were the strongest predictors of death. In the context of treatment of MDR-TB, fluoroquinolones significantly improve survival [111] and antiretroviral therapy substantially reduces mortality among HIV-TB co-infected patients [152]. It has been established that previous TB treatment and previous default from TB treatment [145,148,151,153] could also be predictors of mortality. However, paradoxically, in a study from Finland [154], a history of previous TB was inversely associated with the risk of death, leaving the role of previous TB as a predictor of unfavorable outcome in TB still questionable.

Accordingly to the published studies, several patient-related variables like advanced age [145–148,153–158], male gender [58,147,154], residence in a rural area [148], intravenous drug abuse [159], daily consumption of alcohol [145,149,155,160], unemployment [149,161,162], and homelessness [162] could be risk factors for death during TB treatment. Several factors reflecting poor nutritional status of the patient such as weight below 35 kg [119,160], cachexia, hypoalbuminemia [158], and anemia [159] have also been demonstrated to increase the odds of death. Prior studies have described that patients with more advanced TB at the time of the diagnosis are most likely at higher risk of death [148,162]. Prolonged duration of symptoms prior to the

initial diagnosis [148], delayed care-seeking [156,157], treatment delay [132], bilateral lung involvement, and cavitary lesions on chest radiograph [148,162] have also been identified as predictors of death during TB treatment. Furthermore, several co-morbidities like malignancies [149,162,163], ischemic heart disease [158,162], chronic lung diseases [162], and non-HIV related immunosuppression [154,158] have appeared as risk factors of death during TB treatment.

In the only published study particularly addressing the risk factors for death during MDR-TB treatment [104] (English-language MEDLINE search in October 2009), use of ofloxacin was found to be protective against mortality. To date, there is no information on death predictors among XDR-TB patients on treatment.

3. AIMS OF THE STUDY

A series of retrospective, cross-sectional studies involving all patients with culture-confirmed pulmonary TB diagnosed in Estonia from January 2003 to December 2005 was designed to characterize the factors behind high proportion of MDR-TB and XDR-TB.

The particular aims of the studies were:

1) to reveal the risk factors for MDR-TB and XDR-TB;
2) to assess the effectiveness of treatment and to find the predictors of poor treatment outcome in MDR-TB and XDR-TB;
3) to elucidate the grounds of treatment default and to clarify the risk factors for treatment default;
4) to estimate the mortality and to find out the factors associated with mortality after treatment default.

4. MATERIALS AND METHODS

4.1. Study population

4.1.1. Risk factors for MDR-TB and XDR-TB (I)

The inclusion criteria for the study population were: 1) culture-confirmed pulmonary TB, 2) clinical or radiological evidence of an active disease, and 3) the disease diagnosed in Estonia from 1 January 2003 to 31 December 2005.

The only exclusion criterion was being a chronic TB case (defined as a patient being still sputum smear- or culture-positive after completing a supervised re-treatment regimen).

4.1.2. Risk factors of poor treatment outcome and treatment default (II, III)

The inclusion criteria for the population of these studies were: 1) culture-confirmed pulmonary TB, 2) clinical or radiological evidence of an active disease, 3) the disease diagnosed in Estonia between 1 January 2003 and 31 December 2005, and 4) having started anti-TB treatment after the diagnosis.

The exclusion criteria of these studies were: 1) chronic cases (defined as patients being still sputum smear- or culture-positive after completing a supervised re-treatment regimen) and 2) patients without a final outcome (transferred out or being still on treatment).

To analyze the risk factors for MDR-TB and XDR-TB and predictors of poor treatment outcome, the patients were divided into three groups: 1) patients with non-MDR-TB, 2) patients with MDR-TB, but without XDR-TB, and 3) patients with XDR-TB. For the analysis of the risk factors for treatment default, the patients were divided into two subgroups: 1) treatment defaulters and 2) non-defaulters (i.e. patients with any of the following treatment outcomes: cured, completed, failed, or died).

4.2. Definitions

Standard WHO definitions for patient categories, treatment outcomes, and MDR-TB and XDR-TB were used [164]. All patients were classified into one of the following two categories: new patients (patients, who had never received anti-TB treatment or those who had received anti-TB treatment for less than 1 month) and patients previously treated for TB (patients who were treated for ≥1 month with first-line or second-line anti-TB drugs).

MDR-TB was defined as TB with simultaneous resistance to isoniazide and rifampicin and XDR-TB was defined as MDR-TB plus resistance to any

fluoroquinolone and to at least one of the three injectable second-line anti-TB drugs (capreomycin, kanamycin, or amikacin) (I, II, III).

The definitions of different treatment outcomes were as follows. In non-MDR-TB, "cured" was the patient, who was initially spreading the *M. tuberculosis*, completed the course of treatment, and had negative culture results from samples collected at the end of his/her treatment. In case of MDR-TB or XDR-TB, "cured" was the patient who completed the treatment accordingly to the country protocol and had been consistently culture-negative (with at least four negative results) for the last 12 months of treatment. "Treatment completed" was the patient, who completed the treatment accordingly to the country protocol but did not meet the definition of cure because of the lack of bacteriological culture after the 5th month of therapy. The treatment outcome was regarded as "successful" for those patients, who were considered as "cured" or "completed" (II).

The TB patient, who died of any reason during the course of TB treatment, had "death" as his/her treatment outcome. Patients, who interrupted their anti-TB treatment for more than 2 consecutive months, were classified as "defaulters". Treatment was considered to have "failed" if two or more of the 5 cultures recorded during the final 12 months of treatment were positive or if any of the final 3 cultures was positive. The treatment outcomes "death", "default", and "failure" were combined as "poor outcome" in the study (II). Any patient, who was transferred outside Estonia during the course of treatment, was qualified as "transfer out" and was excluded from analysis according to the protocol.

Treatment effectiveness was defined as the proportion of all patients with a successful outcome. The clinical efficacy of the DOTS-Plus treatment programme was measured as the proportion of all patients with a successful outcome excluding defaulters (II).

4.3. Laboratory methods

Laboratory tests were performed by quality-assured laboratories according to the WHO recommendations [165]. Cultures were performed on conventional Löwenstein-Jensen solid media and in BACTEC® broth media using fluorometric BACTEC® MGIT960 system or BACTEC® 460 radiometric system (Becton Dickinson Diagnostic System, Sparks, MD, USA). Drug susceptibility testing was performed as an indirect test by the proportion method. All strains were tested for susceptibility to rifampicin (2.0 μg/mL), isoniazid (0.2 μg/mL), streptomycin (4.0 μg/mL), ethambutol (5.0 μg/mL), and pyrazinamide (100.0 μg/mL). Resistance was defined as the growth of >1% of the colonies in the drug-containing media, compared with the growth in the drug-free (control) medium. Always, when resistance was found to isoniazid or rifampicin, the respective isolate was tested for resistance against second-line drugs: capreomycin (5 μg/mL), amikacin (2.0 μg/mL), kanamycin (5.0 μg/mL),

prothionamide (5 μg/mL), and ofloxacin (2.0 μg/mL). Quality-assurance for the drug susceptibility testing was done by WHO's Supranational Reference Laboratory in Stockholm, Sweden.

For genotyping of the isolates, *IS6110*-based restriction fragment length polymorphism (RFLP) technique was used. The strains were spoligotyped as described by Kamerbeek *et al*. using commercially available membranes (Isogen, Maarssen, The Netherlands) [166]. The genotype families were defined based on published spoligotype profiles [167]. The clusters were defined as groups of strains with 100% identical *IS6110* patterns.

4.4. Treatment

The regimens to treat MDR-TB and XDR-TB cases were tailored individually on the basis of the DST results. Typically, the treatment regimen contained at least four oral drugs used daily for the full course of treatment and an injectable medication until the monthly *M. tuberculosis* culture converted to negative. After the culture conversion, the injectable medication was continued for three to five times weekly for additional 2–3 months and discontinued thereafter. Typically, the initial treatment for MDR-TB patients was provided on an in-patient basis and after the culture conversion, the patients were followed-up in an outpatient care under direct observation. During the outpatient treatment, the patients received nutritional support (mean value 2.5 US$ per day) and transportation reimbursement for the clinic visits. The treatment continued for 12–18 months after the *M. tuberculosis* culture conversion, which was regularly pursued by *M. tuberculosis* smears and cultures up to the end of treatment. During the study period, Estonia had a full access to all categories of second-line drugs and all TB drugs were available only through the NTP.

4.5. Data collection

A special database of the retrospectively collected information on all patients was developed. The doctors responsible for management of the patients collected the original data using standard forms. The data about previous anti-TB treatment, HIV status, and alcohol abuse originated from patients' medical records, whereas bacteriological data were extracted from the bacteriological laboratory reports. The data collected by the doctors were forwarded to the Tuberculosis Registry assistant, who entered all data into the Tuberculosis Registry database. The latter served as a source for creating database for the current studies. Thereafter, additional efforts were made by the author to supplement any missing data with information extracted directly from patients' medical charts and laboratory reports.

Patients' characteristics were classified into three sets of variables: 1) demographic, 2) socio-economic, and 3) TB-related variables with patients' HIV-status. The demographic characteristics included age, gender, education (basic, secondary, or university), place of birth (Estonia or other), and place of residence at the diagnosis of TB (urban or rural). The socio-economic variables included marital status (married/living as married or single/divorced/widowed), living conditions (with permanent place of living or homeless), previous imprisonment, employment, presence of health insurance, and alcohol abuse. The latter was defined as either registered alcoholism or any mention of medically significant excessive alcohol use in the medical record. The TB-related data included previous anti-TB treatment, presence of a known TB contact, acid-fast bacilli (AFB) smear result, and presence of cavitations on chest X-ray performed at the time of the diagnosis of TB, belonging of *M. tuberculosis* to the W-Beijing genotype family, resistance to all tested first- and second-line TB drugs, and the case detection method. Passive case detection was defined as detection after the patient contacted medical care because of his/her symptoms. In active case finding, the cases were diagnosed by contact tracing or regular chest X-ray screening of people at risk of exposure to TB in occupational settings, prisoners, HIV-infected persons, and shelters' inhabitants. All patients were tested for HIV at the time the diagnosis of TB was made.

The causes of treatment default were drawn by inquiring the responsible doctors. To trace the defaulters, the local TB doctors contacted directly the patients or their families and the dates and causes of death of the defaulters were checked from the Estonian Registry of the Causes of Death. The cause of death was defined as main clinical condition causing death accordingly to the International Classification of Diseases, release 10.

4.6. Statistical analysis

Comparisons of demographic, socio-economic, HIV-status and TB-related characteristics, as well as parameters of treatment outcome between patients' subgroups were performed using Pearson's χ^2 test for categorical variables and Mann-Whitney U-test for continuous variables. Statistical significance was set at $p < 0.05$.

To estimate the predictors of either MDR/non-XDR-TB or XDR-TB (I), a full multinomial logistic regression model with Wald statistical criteria was used covering the variables in the three sets of indicators: patients' demographics, socio-economic characteristics, and TB-related data including HIV-status.

To estimate the predictors of poor treatment outcome (II) and risk factors of treatment default (III), multivariate logistic regression analysis with Wald statistical criteria using backward elimination method was performed covering the variables in the two models of predictors: 1) patients' HIV-status, demographic and socio-economic characteristics and 2) TB-related data (in the

analysis of factors behind poor treatment outcome) and 1) demographic and socio-economic variables and 2) HIV-status, alcohol abuse, and TB-related characteristics (in the analysis of risk factors for treatment default).

To estimate the risk factors for both all-cause and TB-related mortality after default (III), Cox regression analysis using Wald statistical criteria and backward elimination method was performed.

Throughout the studies, for variables with missing information, the statistical analysis was performed for cases with complete information. All analyses were performed with SPSS statistical package, version 10.1 (Chicago, IL, USA).

4.7. Ethics

The study protocol was approved by the Ethics Committee on Human Research at the University of Tartu.

5. RESULTS

5.1. Risk factors for MDR-TB and XDR-TB (I)

5.1.1. Study population

A total of 1163 patients were included, 935 (80.4%) new cases and 228 (19.6%) previously treated cases. Of the included patients, 907 (78.0%) had non-MDR-TB and 256 (22.0%) had MDR-TB (Figure 4). Sixty patients with MDR-TB (23.4%) had XDR-TB (5.2% of the whole study population) and 196 patients (76.6% of the MDR-TB patients and 16.9% of the whole study population) were ill with MDR-TB/non-XDR-TB (Tables 2 and 3). A total of 722 patients (62.1% of the whole study population) were susceptible to all first-line drugs, whereas the MDR-TB cases were resistant on average to 5.7 (range, 2–10) and XDR-TB cases to 6.9 (range, 5–10) anti-TB drugs.

Patients' median age was 45.3 yr (IQR 35.8–55.3); 45.6 yr for male (IQR 37.3–54.6) and 43.3 yr for female patients (IQR 30.5–56.4). The majority of all patients were men (843 patients, 72.5%) and born in Estonia (917 patients, 78.9%). Of all patients, 92 (7.9%) were homeless, 463 patients (39.8%) were unemployed, and 228 (19.6%) had a history of previous imprisonment. Alcohol abuse was reported for 462 cases (39.7%). Among the patients with previously treated TB (n = 228), there were 44 previous treatment defaulters (19.3%) and 14 patients with "failure" as their previous treatment outcome (6.1%). The proportion of alcohol abusers was 61.4% (27/44) among the previous defaulters and 71.4% (10/14) among the patients with previous outcome "failure". Among the new cases, 36.6% (342/935) were alcohol abusers, whereas among relapses, this proportion was 48.2% (82/170). Of all TB cases, 877 (75.4%) were passively detected following patients' referral with their symptoms, 674 (58.0%) were smear-positive for acid-fast bacilli, and 810 (69.7%) had cavitations on their chest radiographs. Of all patients, only 54 (4.7%) were HIV-infected.

Among the XDR-TB patients, who were never previously treated for TB, 40.0% (8/20) were female, but among the relapses, only 17.5% (7/40) were female. Alcohol abuse was reported in 50.0% of new XDR-TB cases (10/20), and in 55.0% of relapses (22/40). Eight out of the 40 XDR-TB patients with previously treated TB (20.0%) were previous treatment defaulters and 3 patients (7.5%) had "treatment failure" as their previous treatment outcome.

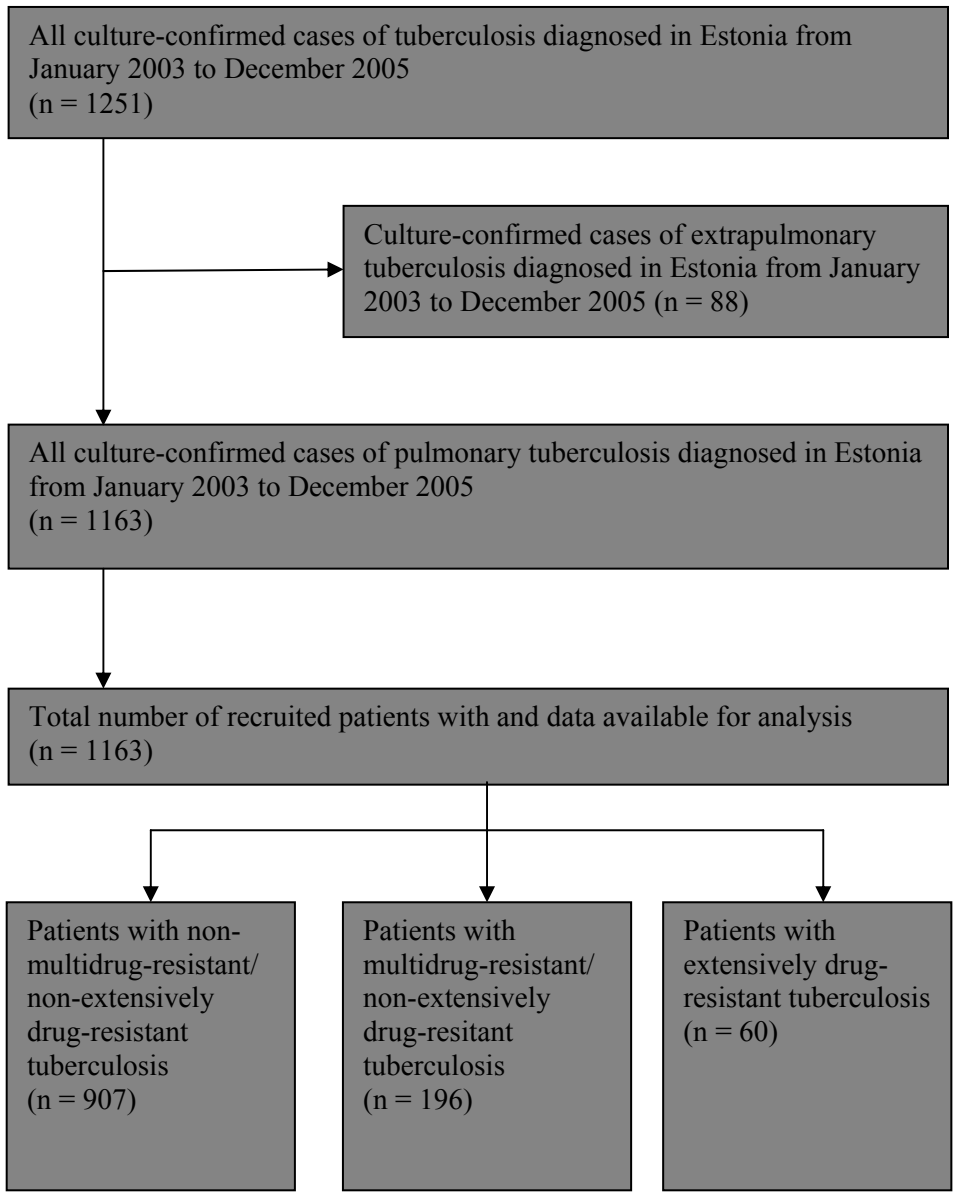

Figure 4. Flow chart of the study population for estimation of the risk factors for multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB). Reproduced with permission from reference I.

Table 2. Demographic and socio-economic characteristics of all patients with culture-confirmed pulmonary non-MDR-TB, MDR-TB/non-XDR-TB, and XDR-TB diagnosed in Estonia from January 2003 to December 2005[a].

Characteristic	Non-MDR-TB patients (n = 907)	MDR-TB/non-XDR-TB patients (n = 196)	XDR-TB patients (n = 60)
Gender			
Male	656 (72.3)	142 (72.5)	45 (75.0)
Female	251 (27.7)	54 (27.5)	15 (25.0)
Age, yr, median (IQR)	46.0 (36.2–55.9)	42.7 (34.5–52	45.0 (34.4–54.2)
≤24	51 (5.6)	15 (7.7)	2 (3.3)
25–44	355 (39.1)	91 (46.4)	26 (43.4)
45–64	376 (41.5)	77 (39.3)	27 (45.0)
≥65	125 (13.8)	13 (6.6)	5 (8.3)
Place of birth			
Estonia	713 (78.6)	159 (81.1)	45 (75.0)
Other	194 (21.4)	37 (18.9)	15 (25.0)
Place of residence			
Urban	606 (66.8)	129 (65.8)	31 (51.7)
Rural	239 (26.4)	54 (27.6)	20 (33.3)
Unknown	62 (6.8)	13 (6.6)	9 (15.0)
Education			
University	53 (5.8)	10 (5.1)	1 (1.7)
Secondary	508 (56.0)	107 (54.6)	33 (55.0)
Basic	332 (36.6)	74 (37.8)	26 (43.3)
Unknown	14 (1.6)	5 (2.5)	0 (0.0)
Marital status			
Married/living as married	395 (43.5)	91 (46.4)	24 (40.0)
Single/divorced/ widowed	505 (55.7)	103 (52.6)	36 (60.0)
Unknown	7 (0.8)	2 (1.0)	0 (0.0)
Place of living			
Permanent	834 (92.0)	182 (92.9)	52 (86.7)
Homeless	71 (7.8)	13 (6.6)	8 (13.3)
Unknown	2 (0.2)	1 (0.5)	0 (0.0)
Activity			
Employed	231 (25.5)	52 (26.5)	12 (20.0)
Unemployed	365 (40.2)	79 (40.3)	19 (31.7)
Other[b]	311 (34.3)	65(33.7)	29 (48.3)
Health insurance			
Yes	530 (58.4)	116 (59.2)	37 (61.7)
No	376 (41.5)	80 (40.8)	23 (38.3)
Unknown	1 (0.1)	0 (0.0)	0 (0.0)
Previous imprisonment			
Yes	169 (18.6)	46 (23.4)	14 (23.3)
No	691 (76.2)	144 (73.5)	44 (73.3)
Unknown	47 (5.2)	6 (3.1)	2 (3.3)
Alcohol abuse			
Yes	336 (37.1)	94 (47.9)	32 (53.3)
No	374 (41.2)	78 (39.8)	18 (30.0)
Unknown	197 (21.7)	24 (12.3)	10 (16.7)

[a]Data are presented as n (%), unless otherwise stated.

[b]Includes retired, disabled, housewife, student, prisoner, and unknown.

IQR, interquartile range; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

Table 3. Tuberculosis (TB)-related data and HIV-status of all patients with culture-confirmed pulmonary non-MDR-TB, MDR-TB/non-XDR-TB, and XDR-TB diagnosed in Estonia from January 2003 to December 2005[a].

Characteristic	Non-MDR-TB patients (n = 907)	MDR-TB/non-XDR-TB patients (n = 196)	XDR-TB patients (n = 60)
Previous TB			
Yes	114 (12.6)	74 (37.8)	40 (66.7)
No	793 (87.4)	122 (62.2)	20 (33.3)
Known TB contact			
Yes	116 (12.8)	27 (13.8)	8 (13.3)
No	702 (77.4)	150 (76.5)	48 (80.0)
Unknown	89 (9.8)	19 (9.7)	4 (6.7)
Cavitation on chest radiograph			
Yes	623 (68.7)	141 (71.9	46 (76.7)
No	275 (30.3)	53 (27.1)	14 (23.3)
Unknown	9 (1.0)	2 (1.0)	0 (0.0)
AFB smear			
Positive	520 (57.3)	117 (59.7)	37 (61.7)
Negative	387 (42.7)	79 (40.3)	23 (38.3)
Case detection			
Active	220 (24.3)	49 (25.0)	16 (26.7)
Passive	686 (75.6)	147 (75.0)	44 (73.3)
Unknown	1 (0.1)	0 (0.0)	0 (0.0)
HIV status			
HIV-seronegative	725 (79.9)	172 (87.7)	47 (78,3)
HIV-seropositive	43 (4.8)	9 (4.6)	2 (3.4)
Unknown	139 (15.3)	15 (7.7)	11 (18.3)

[a]Data are presented as n (%).

AFB, acid-fast bacilli; HIV, human immunodeficiency virus; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis

5.1.2. Risk factors for XDR-TB (I)

The independent risk factors associated with XDR-TB were previous anti-TB treatment [odds ratio (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) (Table 4). Additional analysis, involving only new cases, identified no determinants for XDR-TB, when compared to non-MDR-TB/non-XDR-TB. However, compared to MDR-TB/non-XDR-TB, birth outside Estonia was a risk factor for having XDR-TB (OR 3.17; 95% CI 1.03–9.76).

5.1.3. Risk factors for MDR-TB/non-XDR-TB (I)

Previous anti-TB treatment increased the odds of multidrug-resistance more than fourfold (OR 4.11; 95% CI 2.77–6.08) as were the odds of MDR-TB increased in age groups ≤ 24 yr (OR 2.57; 95% CI 1.09–6.06), 25–44 yr (OR 2.64; 95% CI 1.35–5.16) and 45–64 yr (OR 2.06; 95% CI 1.06–3.99) (Table 5).

In the age group ≤ 24 yr, there was a female predominance (57.1%) that was different from the proportion of women in the general study population (38.0%) ($p < 0.001$, χ^2 test). In this youngest age group, 26 of the non-MDR-TB/non-XDR-TB patients (51.0%) were female, but 66.7% (10 patients) of the MDR-TB/non-XDR-TB patients and all XDR-TB patients (n = 2) were female. Among the patients ≤ 24 yr of age, female gender (OR 6.23; 95% CI 1.02–37.99) and place of birth outside Estonia (OR 82.04; 95% CI 3.46–1945.47) were associated with MDR-TB (Table 6).

Table 4. Demographic, socio-economic, HIV- and tuberculosis (TB)-related factors associated with XDR-TB and MDR-TB among all patients with culture-confirmed pulmonary MDR-TB, diagnosed in Estonia from January 2003 to December 2005, multivariate analysis.

Characteristic	Adjusted[a] OR[b] (95% CI)	p-value	Adjusted[a] OR[c] (95% CI)	p-value	Adjusted[a] OR[d] (95% CI)	p-value
Demographic characteristics						
Gender						
Male	0.96 (0.67–1.39)	0.84	0.99 (0.52–1.90)	0.98	1.03 (0.51–2.10)	0.94
Female	1.0		1.0		1.0	
Age, yr						
≤ 24	2.57 (1.09–6.06)	0.031	1.05 (0.19–5.78)	0.96	0.41 (0.06–2.60)	0.34
25–44	2.64 (1.35–5.16)	0.004	2.16 (0.76–6.14)	0.149	0.82 (0.25–2.70)	0.74
45–64	2.06 (1.06–3.99)	0.033	1.50 (0.53–4.22)	0.44	0.73 (0.22–2.39)	0.60
≥ 65	1.0		1.0		1.0	
Place of birth						
Other	1.14 (0.75–1.74)	0.53	1.69 (0.87–3.31)	0.125	1.48 (0.70–3.13)	0.31
Estonia	1.0		1.0		1.0	
Education						
Basic	1.17 (0.56–2.45)	0.68	3.44 (0.45–26.46)	0.24	2.95 (0.35–24.74)	0.32
Secondary	0.97 (0.47–2.00)	0.93	2.59 (0.34–19.67)	0.36	2.67 (0.32–22.07)	0.36
University	1.0		1.0		1.0	
Place of residence						
Urban	0.89 (0.62–1.29)	0.54	0.60 (0.33–1.11)	0.102	0.67 (0.34–1.33)	0.25
Rural	1.0		1.0		1.0	
Socio-economic characteristics						
Place of living						
Homeless	0.95 (0.47–1.92)	0.89	2.73 (1.15–6.48)	0.022	2.87 (1.03–7.97)	0.43
Permanent	1.0		1.0		1.0	
Activity						
Unemployed	1.08 (0.63–1.87)	0.78	0.54 (0.22–1.28)	0.160	0.50 (0.19–1.30)	0.152
Employed	1.0		1.0		1.0	

Characteristic	Adjusted[a] OR[b] (95% CI)	p-value	Adjusted[a] OR[c] (95% CI)	p-value	Adjusted[a] OR[d] (95% CI)	p-value
Previous imprisonment						
Yes	1.34 (0.87–2.06)	0.185	1.44 (0.74–2.80)	0.29	1.07 (0.51–2.25)	0.85
No	1.0		1.0		1.0	
Health insurance						
Yes	1.38 (0.79–2.41)	0.26	1.25 (0.51–3.06)	0.62	0.91 (0.34–2.44)	0.85
No	1.0		1.0		1.0	
Alcohol abuse						
Yes	1.38 (0.95–1.99)	0.092	1.98 (1.08–3.64)	0.026	1.44 (0.74–2.82)	0.28
No	1.0		1.0		1.0	
Living alone						
Single/divorced/widowed	0.83 (0.59–1.17)	0.29	1.06 (0.59–1.90)	0.86	1.27 (0.67–2.42)	0.46
Married/living as married	1.0		1.0		1.0	
HIV status and TB-related characteristics						
HIV status						
HIV-seropositive	1.57 (0.80–3.11)	0.193	3.12 (1.31–7.41)	0.010	1.98 (0.77–5.08)	0.155
HIV-seronegative	1.0		1.0		1.0	
Previous TB						
Yes	4.11 (2.77–6.08)	<0.001	10.54 (5.97–18.62)	<0.001	2.57 (1.40–4.72)	0.002
No	1.0		1.0		1.0	
Known contact with TB						
Yes	0.90 (0.55–1.47)	0.66	1.39 (0.68–2.81)	0.37	1.55 (0.71–3.39)	0.28
No	1.0		1.0		1.0	
Acid-fast bacilli smear						
Positive	1.06 (0.71–1.58)	0.77	1.05 (0.56–1.97)	0.87	0.99 (0.51–1.95)	0.98
Negative	1.0		1.0		1.0	
Cavitation on chest radiograph						
Yes	1.25 (0.81–1.94)	0.31	1.23 (0.63–2.39)	0.54	0.98 (0.48–2.02)	0.96
No	1.0		1.0		1.0	

Characteristic	Adjusted[a] OR[b] (95% CI)	p-value	Adjusted[a] OR[c] (95% CI)	p-value	Adjusted[a] OR[d] (95% CI)	p-value
Case detection						
Active	0.93 (0.62–1.40)	0.74	0.60 (0.33–1.10)	0.097	0.64 (0.33–1.24)	0.188
Passive	1.0		1.0		1.0	

[a]Full multinomial logistic regression model, each odds ratio (OR) has been adjusted for all other characteristics in the respective subset of variables.
[b]Comparison of MDR-TB/non-XDR-TB against non-MDR/non-XDR-TB.
[c]Comparison of XDR-TB against non-MDR-TB/non-XDR-TB.
[d]Comparison of XDR-TB against MDR-TB/non-XDR-TB.
CI, confidence interval; HIV, human immunodeficiency virus; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

Table 5. Demographic, socio-economic, HIV- and tuberculosis (TB)-related factors associated with XDR-TB and MDR-TB among all patients with culture-confirmed pulmonary MDR-TB, diagnosed in Estonia from January 2003 to December 2005, univariate analysis.

Characteristic	Crude[a] OR[b] (95% CI)	p-value	Crude[a] OR[c] (95% CI)	p-value	Crude[a] OR[d] (95% CI)	p-value
Demographic Characteristics						
Gender						
Male	1.01 (0.71–1.42)	0.97	1.15 (0.63–2.10)	0.65	1.14 (0.59–2.21)	0.70
Female	1.0		1.0		1.0	
Age, yr						
≤ 24	2.54 (1.13–5.70)	0.024	0.76 (0.14–4.04)	0.75	0.30 (0.05–1.82)	0.190
25–44	2.48 (1.31–4.69)	0.005	1.79 (0.68–4.75)	0.24	0.72 (0.02–2.23)	0.57
45–64	1.97 (1.04–3.75)	0.039	1.58 (0.59–4.21)	0.36	0.80 (0.03–2.49)	0.70
≥ 65	1.0		1.0		1.0	
Place of birth						
Other	0.88 (0.59–1.30)	0.52	1.26 (0.67–2.31)	0.46	1.43 (0.72–2.84)	0.30
Estonia	1.0		1.0		1.0	
Education						
Basic	1.18 (0.57–2.43)	0.65	4.15 (0.55–31.23)	0.167	3.51 (0.43–28.80)	0.24
Secondary	1.12 (0.55–2.26)	0.76	3.44 (0.46–25.68)	0.23	3.08 (0.38- 24.99)	0.29
University	1.0		1.0		1.0	
Place of residence						
Urban	0.94 (0.66–1.34)	0.74	0.61 (0.34–1.09)	0.097	0.65 (0.34–1.24)	0.189
Rural	1.0		1.0		1.0	
Socio-economic characteristics						
Place of living						
Homeless	0.84 (0.46–1.55)	0.58	1.81 (0.83–3.96)	0.138	2.15 (0.85–5.48)	0.107
Permanent	1.0		1.0		1.0	
Activity						
Unemployed	1.01 (0.74–1.38)	0.96	0.69 (0.39–1.20)	0.186	0.68 (0.37–1.26)	0.22
Employed	1.0		1.0		1.0	

Characteristic	Crude[a] OR[b] (95% CI)	p-value	Crude[a] OR[c] (95% CI)	p-value	Crude[a] OR[d] (95% CI)	p-value
Previous imprisonment						
Yes	1.27 (0.87–1.85)	0.21	1.30 (0.70–2.43)	0.41	1.03 (0.52–2.04)	0.94
No	1.0		1.0		1.0	
Health insurance						
Yes	1.03 (0.75–1.41)	0.86	1.14 (0.67–1.95)	0.63	1.11 (0.61–2.01)	0.73
No	1.0		1.0		1.0	
Alcohol abuse						
Yes	1.34 (0.96–1.87)	0.085	1.98 (1.09–3.59)	0.025	1.48 (0.77–2.83)	0.24
No	1.0		1.0		1.0	
Living alone						
Single/divorced/widowed	0.89 (0.65–1.21)	0.44	1.17 (0.69–2.00)	0.56	1.33 (0.74–2.39)	0.35
Married/living as married	1.0		1.0		1.0	
HIV status and TB-related characteristics						
HIV status						
HIV-seropositive	0.88 (0.42–1.85)	0.74	0.73 (0.17–3.13)	0.68	0.83 (0.17–3.98)	0.82
HIV-seronegative	1.0		1.0		1.0	
Previous TB						
Yes	4.22 (2.98–5.98)	<0.001	13.91 (7.86–24.64)	<0.001	3.30 (1.79–6.07)	<0.001
No	1.0		1.0		1.0	
Known contact with TB						
Yes	0.74 (0.45–1.22)	0.24	0.72 (0.30–1.71)	0.45	0.97 (0.37–2.56)	0.95
No	1.0		1.0		1.0	
Acid-fast bacilli smear						
Positive	1.10 (0.81–1.51)	0.54	1.20 (0.70–2.05)	0.51	1.09 (0.60–1.97)	0.79
Negative	1.0		1.0		1.0	
Cavitation on chest radiograph						
Yes	1.17 (0.83–1.66)	0.36	1.45 (0.78–2.68)	0.24	1.24 (0.63–2.43)	0.54
No	1.0		1.0		1.0	

Characteristic	Crude[a] OR[b] (95% CI)	p-value	Crude[a] OR[c] (95% CI)	p-value	Crude[a] OR[d] (95% CI)	p-value
Case detection						
Active	0.96 (0.67–1.38)	0.83	0.88 (0.49–1.59)	0.68	0.92 (0.48–1.77)	0.80
Passive	1.0		1.0		1.0	

[a]Full multinomial logistic regression model.
[b]Comparison of MDR-TB/non-XDR-TB against non-MDR/non-XDR-TB.
[c]Comparison of XDR-TB against non-MDR-TB/non-XDR-TB.
[d]Comparison of XDR-TB against MDR-TB/non-XDR-TB.
CI, confidence interval; HIV, human immunodeficiency virus; MDR-TB, multidrug-resistant tuberculosis; OR, odds ratio; XDR-TB, extensively drug-resistant tuberculosis.

Table 6. Demographic factors associated with MDR-TB among all patients less than 25 years with culture-confirmed pulmonary tuberculosis diagnosed in Estonia from January 2003 to December 2005[a].

Characteristic	Crude OR[a] (95% CI)	p-value	Adjusted OR[b] (95% CI)	p-value
Gender				
Female	2.27 (0.71–7.33)	0.169	6.23 (1.02–37.99)	0.048
Male	1.0		1.0	
Place of birth				
Other	4.21 (0.55–32.56)	0.168	82.04 (3.46–1945.47)	0.006
Estonia	1.0		1.0	
Education				
Basic	0.35 (0.20–6.13)	0.47	0.37 (0.19–7.09)	0.51
Secondary	0.15 (0.08–2.83)	0.21	0.11 (0.05–2.36)	0.157
University	1.0		1.0	
Place of residence				
Urban	0.55 (0.16–1.90)	0.34	0.22 (0.46–1.08)	0.062
Rural	1.0		1.0	

[a] Full multinomial logistic regression model, represents comparison of MDR-TB/non-XDR-TB against non-MDR-TB/non-XDR-TB; results of analyses involving XDR-TB are not shown because of low confidence due to the low number of patients in this subgroup (n = 2).

[b] Full multinomial logistic regression model, each odds ratio (OR) has been adjusted for all other characteristics in the table.

CI, confidence interval; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

5.2. Risk factors of poor treatment outcome and treatment default (II, III)

5.2.1. Study population

Of the 1163 patients with culture-confirmed pulmonary TB diagnosed in Estonia from January 2003 to December 2005, 48 died and 6 defaulted before starting TB treatment, hence, 1109 patients were initially included in the cohort for assessment of the risk factors of poor treatment outcome and treatment default. Two patients were transferred out thereafter and treatment outcomes were thus assessed for 872 non-MDR-TB and 235 MDR-TB patients (Figure 5). The proportion of XDR-TB among the MDR-TB patients was 23.0% (54/235).

Patients' median age was 43.2 yr (range, 15–80) being 44.5 yr for males (range, 22–79) and 38.2 yr for females (range, 15–80). At the start of treatment, 186 of all MDR-TB cases (79.1%) had resistance to all first-line anti-TB drugs. The patients with MDR-TB had median resistance to 5.0 anti-TB drugs (range, 2–10), whereas those with XDR-TB had median resistance to 7.0 drugs (range, 5–10, $p < 0.001$ vs. MDR-TB) (Table 7).

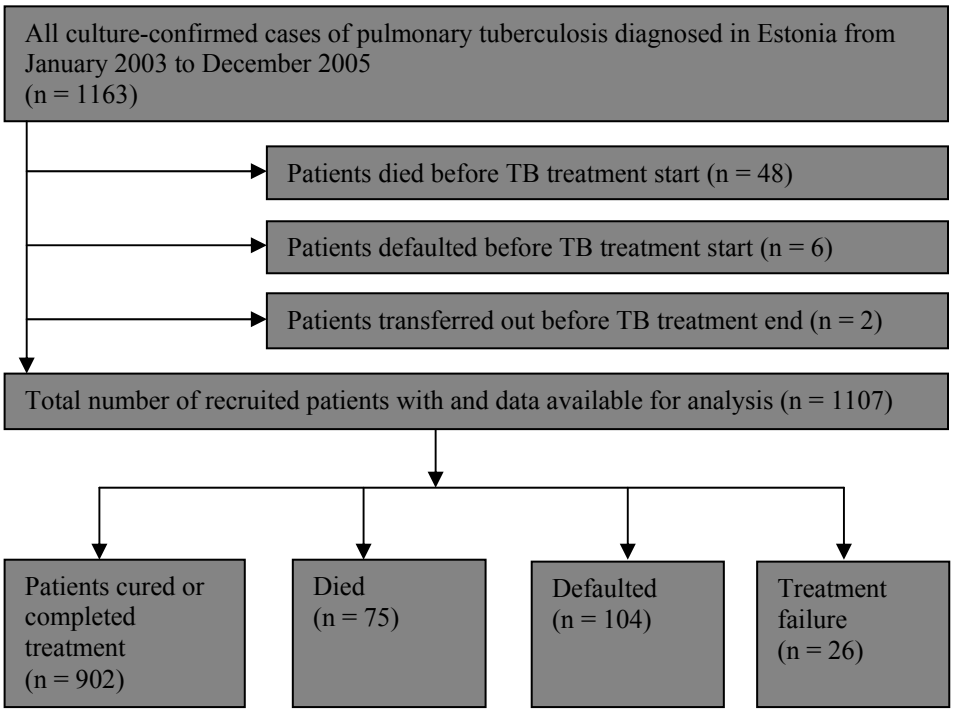

Figure 5. Flow chart of the study population for estimation of the risk factors for poor tuberculosis (TB) treatment outcome and treatment default (II, III). Reproduced with permission from reference III.

Table 7. Drug resistance at the start of treatment of all patients with culture-confirmed pulmonary MDR-TB, XDR-TB, and non-MDR-TB, who started tuberculosis treatment in Estonia from January 2003 to December 2005.

	MDR-TB n = 235	XDR-TB n = 54	Non-MDR-TB n = 872
First-line drugs			
Isoniazid	235 (100.0)	54 (100.0)	106 (12.2)
Rifampicin	235 (100.0)	54 (100.0)	2 (0.2)
Streptomycin	220 (93.6)	49 (90.7)	141 (16.2)
Pyrazinamide	63 (26.8)	13 (24.1)	4 (0.5)
Ethambutol	215 (91.5)	53 (98.1)	19 (2.2)
To all first-line drugs	186 (79.1)	46 (85.2)	0 (0)
Second-line drugs			
Amikacin	32 (13.6)	15 (27.8)	4 (0.5)
Capreomycin	34 (14.5)	11 (20.4)	4 (0.5)
Kanamycin	153 (65.1)	53 (98.1)	7 (0.8)
Ofloxacin	68 (28.9)	54 (100.0)	4 (0.5)
Protionamide	64 (27.2)	20 (37.0)	23 (2.6)

Data are presented as n (%).
MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

5.2.2. Treatment outcomes (II)

In the 235 patients with MDR-TB, the proportion of patients with successful treatment outcome was 60.4% and the clinical efficacy of the treatment was 72.8% (Table 8). When compared to the patients with previously treated TB, those not previously treated for TB had significantly higher proportion of successful treatment (71.0% vs. 47.1%, OR 2.75; 95% CI 1.60–4.72), significantly lower proportion of treatment failures (4.6% vs. 15.4%, OR 0.26; 95% CI 0.10–0.70), and significantly lower mortality (7.6% vs. 20.2%, OR 0.33; 95% CI 0.15–0.73).

In the XDR-TB patients, the proportions of successful treatment outcome and treatment clinical efficacy were 42.6% and 50.0%, respectively. Among the new XDR-TB cases, the proportion of defaulters was non-significantly higher than that in the previously treated cases (21.1% vs. 11.4%; $p = 0.34$, but the mortality was slightly lower (15.8% vs. 28.6%; $p = 0.70$). Compared to the patients with MDR-TB, those with XDR-TB expectedly had significantly lower proportion of successful treatment outcome (OR 0.39; 95% CI 0.21–0.72) and significantly lower clinical efficacy of the treatment (OR 0.25; 95% CI 0.13–0.51).

Table 8. Treatment outcome of all patients with culture-confirmed pulmonary MDR-TB (n = 235), XDR-TB (n = 54), and non-MDR-TB (n = 872), who started tuberculosis (TB) treatment in Estonia from January 2003 to December 2005.

Outcome	Cure	Completion	Death	Failure	Default
MDR-TB					
Never treated for TB	89 (67.9)	4 (3.1)	10 (7.6)	6 (4.6)	22 (16.8)
Previously treated for TB	46 (44.2)	3 (2.9)	21 (20.2)	16 (15.4)	18 (17.3)
Total	135 (57.4)	7 (3.0)	31 (13.2)	22 (9.4)	40 (17.0)
OR (95% CI)[a]	0.37 (0.22–0.64)	0.94 (0.21–4.31)	3.06 (1.37–6.84)	3.79 (1.43–10.06)	1.04 (0.52–2.06)
p-value[a]	<0.001	0.94	0.005	0.005	0.92
XDR-TB					
Never treated for TB	8 (42.1)	1 (5.3)	3 (15.8)	3 (15.8)	4 (21.0)
Previously treated for TB	14 (40.0)	0	7 (28.6)	10 (20.0)	4 (11.4)
Total	22 (40.7)	1 (1.9)	10 (18.5)	13 (24.1)	8 (14.8)
OR (95% CI)[b]	0.92 (0.30–2.85)	0.95 (0.85–1.05)	1.33 (0.30–5.89)	2.13 (0.51–8.96)	0.48 (0.11–2.21)
p-value[b]	0.88	0.17	0.70	0.29	0.34
Non-MDR-TB					
Never treated for TB	655 (85.7)	26 (3.4)	35 (4.6)	0	48 (6.3)
Previously treated for TB	72 (66.7)	7 (6.5)	9 (8.3)	4 (3.7)	16 (14.8)
Total	727 (83.4)	33 (3.8)	44 (5.0)	4 (0.5)	64 (7.3)
OR (95% CI)[c]	0.33 (0.21–0.52)	1.97 (0.83–4.65)	1.89 (0.88–4.06)	1.04 (1.00–1.08)	2.59 (1.42–4.76)
p-value[c]	0.001	0.12	0.10	0.001	0.001

Data are presented as n (%), unless otherwise stated.

[a] Comparison between "never treated" vs. "previously treated" MDR-TB patients.

[b] Comparison between "never treated" vs. "previously treated" XDR-TB patients.

[c] Comparison between "never treated" vs. "previously treated" non-MDR-TB patients.

CI, confidence interval; MDR-TB, multidrug-resistant tuberculosis; OR, odds ratio; XDR-TB, extensively drug-resistant tuberculosis.

5.2.3. Risk factors associated with poor treatment outcome in MDR-TB patients (II)

In the MDR-TB patients, HIV-infection increased the risk of poor treatment outcome tenfold (OR 10.16; 95% CI 1.17–88.84) and previous TB treatment almost threefold (OR 2.88; 95% CI 1.50–5.52) (Tables 9 and 10). Resistance to ofloxacin (OR 2.30; 95% CI 1.17–4.51) and positive AFB smear (OR 2.09; 95% CI 1.04–4.20) at the start of anti-TB treatment were independent risk factors of poor treatment outcome in MDR-TB. Alcohol abuse ($p = 0.07$) was close to being significantly associated with poor treatment outcome in MDR-TB.

5.2.4. Risk factors associated with poor treatment outcome in XDR-TB patients (II)

In the XDR-TB patients, living in an urban area (OR 19.76; 95% CI 1.98–197.01) was associated with poor treatment outcome in XDR-TB (Tables 11 and 12). Also, the patients with a positive AFB smear result at the start of treatment were more likely to have poor treatment outcome, compared to those with a negative AFB smear result (OR 3.64; 95% CI 1.03–12.88).

Table 9. Demographic, socio-economic, and HIV-related risk factors associated with poor treatment outcome in all MDR-TB patients, who started tuberculosis treatment in Estonia from January 2003 to December 2005 (n = 235).

Characteristic	Crude OR (95% CI)	p-value	Adjusted OR[a] (95% CI)	p–value
Gender				
Male	1.87 (1.01–3.45)	0.05	–	–
Female	1.0			
Age, yr				
≤ 24	0.42 (0.08–2.20)	0.30	0.24 (0.02–3.23)	0.28
25–44	1.13 (0.36–3.60)	0.83	0.86 (0.15–5.00)	0.87
45–64	1.48 (0.46–4.75)	0.51	1.74 (0.30–10.04)	0.53
≥ 65	1.0		1.0	
Place of birth				
Other	1.37 (0.71–2.62)	0.35	–	–
Estonia	1.0			
Education				
Basic	1202 (0.00–>1000)	0.54	–	–
Secondary	818 (0.00–>1000)	0.56	–	–
University	1.0			
Place of residence				
Urban	1.35 (0.75–2.42)	0.33	1.74 (0.83–3.62)	0.14
Rural	1.0		1.0	
Place of living				
Homeless	1.80 (0.67–4.83)	0.25	–	–
Permanent	1.0			
Activity				
Unemployed	1.65 (0.96–2.82)	0.07	–	–
Employed	1.0			
Previous imprisonment				
Yes	1.56 (0.84–2.87)	0.16	–	–
No	1.0			
Health insurance				
Yes	0.72 (0.42–1.23)	0.23	–	–
No	1.0			
Alcohol abuse				
Yes	2.42 (1.34–4.37)	0.003	1.94 (0.96–3.92)	0.07
No	1.0		1.0	
Living alone				
Single/divorced/widowed	1.00 (0.59–1.69)	0.99	–	–
Married/living as married	1.0			
HIV status				
HIV-seropositive	3.32 (0.81–13.67)	0.10	10.16 (1.17–88.84)	0.04
HIV-seronegative	1.0		1.0	

The data were analyzed using multivariate logistic regression.

[a]Each odds ratio (OR) has been adjusted for all other characteristics in the table.

CI, confidence interval; HIV, human immunodeficiency virus; MDR-TB, multidrug-resistant tuberculosis.

Table 10. Tuberculosis (TB)-related risk factors associated with poor treatment outcome in all MDR-TB patients, who started TB treatment in Estonia from January 2003 to December 2005 (n = 235).

Characteristic	Crude OR (95% CI)	p-value	Adjusted OR[a] (95% CI)	p–value
Previous TB				
Yes	2.75 (1.60–4.71)	<0.001	2.88 (1.50–5.52)	0.001
No	1.0		1.0	
AFB smear				
Positive	2.07 (1.19–3.60)	0.01	2.09 (1.04–4.20)	0.04
Negative	1.0		1.0	
Cavitation on chest radiograph				
Yes	1.71 (0.92–3.17)	0.09	1.75 (0.79–3.87)	0.17
No	1.0		1.0	
W-Beijing genotype				
Yes	0.71 (0.42–1.19)	0.19	0.59 (0.31–1.10)	0.09
No	1.0		1.0	
Case detection				
Active	1.11 (0.61–2.03)	0.73	–	–
Passive	1.0			
Known contact with TB				
Yes	0.88 (0.37– 2.10)	0.77	–	–
No	1.0			
Resistance to all first-line TB drugs				
Yes	0.94 (0.49–1.78)	0.84	–	–
No	1.0			
Resistance to ofloxacin				
Yes	2.56 (1.44–4.55)	0.001	2.30 (1.17–4.51)	0.02
No	1.0		1.0	
Resistance to amikacin				
Yes	1.90(0.90–4.03)	0.09	–	–
No	1.0			
Resistance to capreomycin				
Yes	1.08 (0.51–2.26)	0.84	–	–
No	1.0			
Resistance to kanamycin				
Yes	1.99 (1.12–3.52)	0.02	–	–
No	1.0			

The data were analyzed using multivariate logistic regression.
[a]Each odds ratio (OR) has been adjusted for all other characteristics in the table.
CI, confidence interval; MDR-TB, multidrug-resistant tuberculosis.

Table 11. Demographic, socio-economic, and HIV-related risk factors associated with poor treatment outcome in all XDR-TB patients, who started tuberculosis treatment in Estonia from January 2003 to December 2005 (n = 54).

Characteristic	Crude OR (95% CI)	p-value	Adjusted OR[a] (95% CI)	p-value
Gender				
Male	2.22 (0.65–7.66)	0.21	–	–
Female	1.0			
Age, yr				
≤ 24	< 0.01 (<0.01–>1000)	0.81	–	–
25–44	< 0.01 (<0.01–>1000)	0.82	–	–
45–64	< 0.01 (<0.01–>1000)	0.82	–	–
≥ 65	1.0			
Place of birth				
Other	1.47 (0.42–5.18)	0.55	14.44 (0.86–241.73)	0.06
Estonia	1.0		1.0	
Education				
Basic	537 (<0.001–>1000)	0.78	–	–
Secondary	851 (<0.001–>1000)	0.76	–	–
University	1.0			
Place of residence				
Urban	3.18 (0.91–11.03)	0.07	19.76 (1.98–197.01)	0.01
Rural	1.0		1.0	
Place of living				
Homeless	0.70 (0.16–3.17)	0.65	–	–
Permanent	1.0			
Activity				
Unemployed	0.89 (0.29–2.80)	0.85	–	–
Employed	1.0			
Previous imprisonment				
Yes	1.04 (0.28–3.83)	0.96	–	–
No	1.0			
Health insurance				
Yes	1.02 (0.34–3.08)	0.98	–	–
No	1.0			

Characteristic	Crude OR (95% CI)	p-value	Adjusted ORa (95% CI)	p-value
Alcohol abuse				
Yes	2.85 (0.79–10.3)	0.11	–	–
No	1.0			
Living alone				
Single/divorced/widowed	0.53 (0.17–1.65)	0.28	–	–
Married/living as married	1.0			
HIV status				
HIV-seropositive	1167 (<0.001–>1000)	0.79	–	–
HIV-seronegative	1.0			

The data were analyzed using multivariate logistic regression.

[a]Each odds ratio (OR) has been adjusted for all other characteristics in the table.

CI, confidence interval; HIV, human immunodeficiency virus; XDR-TB, extremely drug-resistant tuberculosis.

Table 12. Tuberculosis (TB)-related risk factors associated with poor treatment outcome in all XDR-TB patients, who started TB treatment in Estonia from January 2003 to December 2005 (n = 54).

Characteristic	Crude OR (95% CI)	p-value	Adjusted OR[a] (95% CI)	p-value
Previous TB				
Yes	1.35 (0.44–4.16)	0.60	–	–
No	1.0			
AFB smear				
Positive	2.67 (0.86–8.23)	0.09	3.64 (1.03–12.88)	0.05
Negative	1.0		1.0	
Cavitation on chest radiograph				
Yes	2.28 (0.62–8.40)	0.22	–	–
No	1.0			
W-Beijing genotype				
Yes	0.76 (0.26–2.23)	0.61	–	–
No	1.0			
Case detection				
Active	1.02 (0.30–3.47)	0.98	–	–
Passive	1.0			
Known contact with TB				
Yes	0.44 (0.07–2.89)	0.39	–	–
No	1.0			
Resistance to all first-line TB drugs				
Yes	0.40 (0.07–2.18)	0.29	0.20 (0.02–1.90)	0.16
No	1.0		1.0	
Resistance to amikacin				
Yes	1.16 (0.35–3.89)	0.81	–	–
No	1.0			
Resistance to capreomycin				
Yes	0.86 (0.23–3.28)	0.83	–	–
No	1.0			
Resistance to kanamycin				
Yes	0.003 (<0.001–>1000)	0.79	–	–
No	1.0			

The data were analyzed using multivariate logistic regression.
[a]Each odds ratio (OR) has been adjusted for all other characteristics in the table.
CI, confidence interval; XDR-TB, extremely drug-resistant tuberculosis.

5.2.5. Treatment default rate and causes of treatment default (III)

In the whole study population (n = 1107), the treatment success rate was 81.5% and the default rate was 9.4% (Table 8). Patients not previously treated for TB had significantly lower treatment default rate than did patients with previously treated TB (7.8% vs. 16.0%; $p < 0.001$, χ^2 test). The treatment default rate was significantly higher in MDR-TB patients than in non-MDR patients (17.0% vs. 7.3%; $p < 0.001$, χ^2 test).

The most common cause of treatment default was alcohol abuse (77.9%) (Table 13). The median duration of treatment from start to the treatment default was 142.5 days (range, 2–994) being 124.5 days for non-MDR-TB (range, 11–450) and 241.5 days for MDR-TB patients (range, 2–994).

Table 13. Reasons behind treatment default of all defaulters (n = 104) with culture-confirmed pulmonary tuberculosis (TB) in Estonia, 2003–2005.

Treatment defaulting causes	n (%)
Alcohol abuse	81 (77.9)
Refusal from TB treatment	12 (11.5)
Concomitant malignant disease	3 (2.9)
Concomitant psychiatric disease	3 (2.9)
Drug abuse	3 (2.9)
Severe TB drugs side effects	1 (1.0)
Patient moved to other county in Estonia	1 (1.0)

5.2.6. Risk factors associated with treatment default (III)

Alcohol abuse (OR 3.22; 95% CI 1.93–5.38) and unemployment (OR 3.05; 95% CI 1.84–5.03) increased the risk of treatment default threefold (Table 14). Also, MDR-TB (OR 2.17; 95% CI 1.35–3.50), urban residence (OR 1.85; 95% CI 1.00–3.42), and previous imprisonment (OR 1.78; 95% CI 1.05–3.03) were risk factors of treatment default. Homelessness ($p = 0.07$) was close to being significantly associated with treatment default.

Predictors of default among the non-MDR-TB patients were unemployment (OR 5.41; 95% CI 2.70–10.8), alcohol abuse (OR 3.81; 95% CI 1.97–7.37), previous TB (OR 2.79; 95% CI 1.40–5.57), and urban residence (OR 2.80; 95% CI 1.16–6.74), whereas patients with positive AFB smear had significantly less likelihood of treatment default (OR 0.47; 95% CI 0.26–0.86) (Table 15). Among the MDR-TB patients, unemployment was a risk factor for default (OR 2.92; 95% CI 1.41–6.04).

Table 14. Risk factors associated with treatment default among all patients with culture-confirmed pulmonary tuberculosis (TB) in Estonia, 2003–2005.

Characteristic	Univariate analysis		Multivariate analysis	
	Crude OR (95% CI)	p-value	Adjusted OR[a] (95% CI)	p-value
Patients' demographic and socio-economic characteristics				
Gender				
Male	0.62 (0.38–1.02)	0.06	–	–
Female	1.0			
Age, yr				
≤ 24	2.35 (0.38–14.35)	0.36	–	–
25–44	7.40 (1.78–30.78)	0.01	–	–
45–64	6.67 (1.60–27.83)	0.01	–	–
≥ 65	1.0			
Place of birth				
Other	1.56 (0.99–2.46)	0.06	1.43 (0.84–2.43)	0.19
Estonia	1.0		1.0	
Education				
Basic	1.87 (0.56–6.28)	0.31	–	–
Secondary	2.23 (0.68–7.32)	0.19	–	–
University	1.0			
Place of residence				
Urban	2.26 (1.28–4.00)	0.005	1.85 (1.00–3.42)	0.049
Rural	1.0		1.0	
Live alone				
Yes	1.57 (1.03–2.39)	0.04	–	–
No	1.0			
Homelessness				
Yes	4.00 (2.34–6.84)	<0.001	1.97 (0.94–4.13)	0.07
No	1.0		1.0	
Unemployment				
Yes	3.53 (2.30–5.43)	<0.001	3.05 (1.84–5.03)	<0.001
No	1.0		1.0	
Presence of health insurance				
No	0.30 (0.20–0.46)	<0.001	–	–
Yes	1.0			
Previous imprisonment				
Yes	2.36 (1.51–3.69)	<0.001	1.78 (1.05–3.03)	0.03
No	1.0		1.0	
HIV-status, alcohol abuse and TB-related characteristics				
Alcohol abuse				
Yes	3.21 (1.99–5.18)	<0.001	3.22 (1.93–5.38)	<0.001
No	1.0		1.0	
HIV status				
HIV-seropositive	1.53 (0.67–3.51)	0.31	–	–
HIV-seronegative	1.0			

Characteristic	Univariate analysis		Multivariate analysis	
	Crude OR (95% CI)	p-value	Adjusted OR[a] (95% CI)	p-value
Previous TB				
Yes	2.25 (1.45–3.50)	<0.001	–	–
No	1.0			
Previous treatment default				
Yes	2.06 (0.89–4.76)	0.09	–	–
No	1.0			
MDR-TB				
Yes	2.59 (1.69–3.96	<0.001	2.17 (1.35–3.50)	0.001
No	1.0		1.0	
XDR-TB				
Yes	1.73 (0.80–3.78)	0.17	–	–
No	1.0			
Beijing genotype				
Yes	2.24 (1.35–3.70)	0.002	–	–
No	1.0			
AFB smear[b]				
Positive	0.76 (0.51–1.14)	0.18	–	–
Negative	1.0			
Cavitation on chest radiograph[b]				
Yes	0.70 80.46–1.07)	0.10	0.65 (0.40–1.06)	0.08
No	1.0		1.0	

The data were analyzed using multivariate logistic regression.

[a]Each odds ratio (OR) has been adjusted for all other characteristics in the respective subset of variables.

[b]At the start of TB treatment.

AFB, acid-fast bacilli; CI, confidence interval; HIV, human immunodeficiency virus; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

Table 15. Risk factors associated with treatment default among all non-MDR-TB and MDR-TB patients with culture-confirmed pulmonary tuberculosis (TB) in Estonia, 2003–2005.

Variable	Non-MDR-TB patients				MDR-TB patients			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)[a]	p-value	OR (95% CI)	p-value	OR (95% CI)[a]	p-value
Patients' demographic and socio-economic characteristics								
Gender								
Male	1.44 (0.78–2.65)	0.25	–		2.00 (0.84–4.77)	0.12	–	
Female	1.0				1.0			
Age, yr								
≤ 24	0.23 (0.03–1.71)	0.15	–		0.74 (0.15–3.56)	0.71	–	
25–44	1.37 (0.82–2.30)	0.23	–		1.17 (0.58–2.36)	0.66	–	
≥ 45	1.0				1.0			
Place of birth								
Other	1.81 (1.04–3.16)	0.04	–		1.24 (0.54–2.83)	0.61	–	
Estonia	1.0				1.0			
Education								
Basic	0.71 (0.41–1.24)	0.23	–		1.19 (0.60–2.37)	0.62	–	
Secondary and university	1.0				1.0			
Place of residence								
Urban	3.36 (1.42–7.98)	0.006	2.80 (1.16–6.74)	0.02	1.69 (0.75–3.81)	0.20	–	
Rural	1.0		1.0		1.0			
Live alone								
Yes	1.96 (1.13–3.41)	0.017	–		1.14 (0.57–2.26)	0.72	–	
No	1.0				1.0			
Homelessness								
Yes	5.93 (3.21–11.0)	<0.001	–		1.56 (0.48–5.04)	0.46	–	
No	1.0				1.0			
Unemployment								
Yes	4.55 (2.57–8.07)	<0.001	5.41 (2.70–10.8)	<0.001	2.77 (1.38–5.55)	0.004	2.92 (1.41–6.04)	0.004
No	1.0		1.0		1.0		1.0	

Variable	Non-MDR-TB patients				MDR-TB patients			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)[a]	p-value	OR (95% CI)	p-value	OR (95% CI)[a]	p-value
Presence of health insurance								
No	0.23 (0.13–0.41)	<0.001	–		0.39 (0.19–0.77)	0.007	–	
Yes	1.0				1.0			
Previous imprisonment								
Yes	2.43 (1.37–4.31)	0.002	–		2.05 (0.98–4.29)	0.06	–	
No	1.0				1.0			
HIV-status, alcohol abuse and TB-related characteristics								
Alcohol abuse								
Yes	3.88 (2.08–7.24)	<0.001	3.81 (1.97–7.37)	<0.001	1.98 (0.92–4.25)	0.08	2.12 (0.93–4.84)	0.07
No	1.0		1.0		1.0		1.0	
HIV status								
HIV-seropositive	2.15 (0.87–5.35)	0.10	–		0.61 (0.07–5.01)	0.64	–	
HIV-seronegative	1.0				1.0			
Previous TB								
Yes	2.59 (1.42–4.75)	0.002	2.79 (1.40–5.57)	0.004	1.04 (0.52–2.06)	0.92	–	
No	1.0				1.0			
Previous default								
Yes	4.42 (1.38–14.13)	0.01	–		0.64 (0.18–2.24)	0.48	–	
No	1.0				1.0			
MDR-TB								
Yes	NA		NA		NA		NA	
No								
XDR-TB								
Yes	NA		NA		0.81 (0.35–1.88)	0.62	–	
No					1.0			

Variable	Non-MDR-TB patients				MDR-TB patients			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)[a]	p-value	OR (95% CI)	p-value	OR (95% CI)[a]	p-value
Beijing genotype								
Yes	1.41 (0.18–11.3)	0.75	–		1.07 (0.54–2.12)	0.85	–	
No	1.0				1.0			
AFB smear[b]								
Positive	0.54 (0.32–0.90)	0.02	0.47 (0.26–0.86)	0.013	1.32 (0.65–2.68)	0.44		
Negative	1.0		1.0		1.0		–	
Cavitation on chest radiograph[b]								
Yes	0.56 (0.34–0.94)	0.03	–		0.94 (0.44–2.02)	0.94	–	
No	1.0				1.0			

The data were analyzed using multivariate logistic regression.

[a]Each odds ratio (OR) has been adjusted for all other characteristics in the respective subset of variables.

[b]At the start of TB treatment.

AFB, acid-fast bacilli; CI, confidence interval; HIV, human immunodeficiency virus; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

5.2.7. Survival after treatment default and predictors of mortality (III)

Out of the 104 defaulters, 102 were successfully traced. Of those, 4 patients (3.9%) cured, 6 (5.9%) were still on treatment at closure of the database (October 31, 2008), and 30 (29.4%) died after default. Of those, who died after the treatment default, 16 patients (53.3%) had their death related with TB. The proportions of MDR-TB among patients, who died after default of whatever cause and of TB, were 40.0% and 68.8%, respectively. Patients' median survival time after their treatment default was 342.0 days (range, 28–1021).

Unemployment was a predictor of both all-cause and TB-related death [hazard ratio (HR) 4.58; 95% CI 1.05–20.1 and HR 11.2; 95% CI 1.58–80.2, respectively], whereas association with HIV-infection was close to being a significant predictor of all-cause deaths ($p = 0.052$) (Table 16). HIV infection, however, was a significant predictor of TB-related mortality (HR 51.2; 95% CI 6.06–432). The other predictors of TB-related mortality included MDR-TB (HR 8.56; 95% CI 1.81–40.4), previous TB (HR 5.15; 95% CI 1.64–16.2), and smear-positive sputum at the start of TB treatment (HR 9.59; 95% CI 1.79–51.4).

Table 16. Risk factors of all-cause and tuberculosis (TB)-related death after treatment default among all patients with culture-confirmed pulmonary TB in Estonia, 2003–2005.

Characteristic	All-cause mortality				TB-related mortality			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI) [a]	p-value	HR (95% CI)	p-value	HR (95% CI)[a]	p-value
Patients' demographic and socio-economic characteristics								
Gender								
Male	1.79 (0.62–5.12)	0.28	–		1.30 (0.37–4.55)	0.69	–	
Female	1.0				1.0			
Age, yr								
≤ 24	0.84 (0.11–6.31)	0.86	–		1.87 (0.23–15.2)	0.56	–	
25–44	0.70 (0.39–1.46)	0.35	–		0.99 (0.36–2.72)	0.98	–	
≥ 45	1.0				1.0			
Place of birth								
Other	2.12 (1.02–4.41)	0.49	2.15 (0.96–4.79)	0.62	1.94 (0.71–5.34)	0.20	–	
Estonia	1.0		1.0		1.0			
Education								
Basic	1.30 (0.63–2.70)	0.49	–		1.49 (0.56–4.02)	0.43	–	
Secondary and university	1.0				1.0			
Place of residence								
Urban	0.87 (0.33–2.30)	0.78	–		0.75 (0.21–2.64)	0.65	–	
Rural	1.0				1.0			
Live alone								
Yes	1.04 (0.49–2.22)	0.92	–		0.70 (0.26–1.88)	0.48	–	
No	1.0				1.0			
Homelessness								
Yes	1.21 (0.52–2.83)	0.66	–		0.91 (0.26–3.21)	0.89	–	
No	1.0				1.0			
Unemployment								
Yes	2.08 (0.85–5.10)	0.11	4.58 (1.05–20.1)	0.04	2.46 (0.70–8.64)	0.16	11.2 (1.58–80.2)	0.016
No	1.0		1.0		1.0		1.0	

Characteristic	All-cause mortality				TB-related mortality			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI) [a]	p-value	HR (95% CI)	p-value	HR (95% CI)[a]	p-value
Presence of health insurance								
No	0.75 (0.34–1.69)	0.49	2.57 (0.73–8.99)	0.14	0.67 (0.22–2.10)	0.49	3.8 (0.84– 17.2)	0.08
Yes	1.0				1.0		1.0	
Previous imprisonment								
Yes	0.73 (0.32–1.65)	0.45	–		1.07 (0.39–2.94)	0.90	–	
No	1.0				1.0			
HIV–status, alcohol abuse and TB–related characteristics								
Alcohol abuse								
Yes	1.61 (0.61–4.26)	0.34	–	–	0.99 (0.31–3.15)	0.98	–	
No	1.0				1.0			
HIV status								
HIV–seropositive	2.82 (0.96–8.24)	0.06	2.93 (0.99–8.57)	0.052	4.31 (1.20–15.5)	0.03	51.2 (6.06–432)	<0.001
HIV–seronegative	1.0		1.0		1.0		1.0	
Previous TB								
Yes	1.48 (0.71–3.08)	0.29	–	–	3.63 (1.32–10.0)	0.013	5.15 (1.64–16.2)	0.005
No	1.0				1.0		1.0	
MDR–TB								
Yes	1.06 (0.51–2.19)	0.89	–	–	3.19 (1.11–9.18)	0.03	8.56 (1.81–40.4)	0.007
No	1.0				1.0		1.0	
XDR–TB								
Yes	1.29 (0.39–4.26)	0.68	–	–	2.45 (0.70–8.60)	0.16	–	
No	1.0				1.0			
Beijing genotype								
Yes	0.64 (0.25–1.68)	0.36	–	–	0.72 (0.21–2.53)	0.61	–	
No	1.0				1.0			
AFB smear[b]								
Positive	1.27 (0.62–2.62)	0.51	–	–	3.95 (1.13–13.9)	0.03	9.59 (1.79–51.4)	0.008
Negative	1.0				1.0		1.0	

Characteristic	All-cause mortality				TB-related mortality			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI) [a]	p-value	HR (95% CI)	p-value	HR (95% CI)[a]	p-value
Cavitation on chest radiograph[b]								
Yes	1.29 (0.60–2.75)	0.52	–	–	4.20 (0.95–18.5)	0.06	–	
No	1.0				1.0			

The data were analyzed using Cox regression.

[a]Each hazard ratio (HR) has been adjusted for all other characteristics in the respective subset of variables.

[b]At the start of TB treatment.

AFB, acid-fast bacilli; CI, confidence interval; HIV, human immunodeficiency virus; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

6. DISCUSSION

6.1. Risk factors for MDR-TB and XDR-TB (I)

The results of our current studies indicate that MDR-TB and XDR-TB share common risk factors, out of which previously treated TB has the strongest association. Regarding MDR-TB, this is in line with the findings of earlier studies performed elsewhere [48,51,56,59,77], but our present results imply that XDR-TB is associated with previous TB even more vigorously than does MDR-TB. In generating extremely resistant strains, the duration of previous TB treatment seems to play a major role, since according to the first published study addressing risk factors for XDR-TB, performed only on re-treated patients [81], the presence of XDR-TB was associated with the cumulative duration of the previous treatment. In the current study, among the non-MDR patients, the re-treatment cases accounted for only 12.6 %, but in MDR-TB and XDR-TB, the respective proportions were 37.8% and 66.7%.

The finding that MDR-TB is strongly associated with age less than 65 yr and that the association is strongest in the age group 25–44 yr is probably related to ongoing transmission of multidrug-resistant *M. tuberculosis* strains in the community. Among the new cases in the present study population, the rate of primary MDR-TB was 15.2%. We currently showed that in age group less than 25 yr, female patients were at six times higher risk of becoming ill with MDR-TB. On the contrary, in a meta-analysis by Faustini *et al.* [56], male gender was found a determinant of MDR-TB in Europe. An association between MDR-TB and female gender in the whole study population has also been described in a few previous studies [49,58,59], but the particularly high MDR-TB risk in younger females has been, to our knowledge, noticed first in our study. Taking into account the type of the society, where males and females have presumably equal accessibility to health services, an explanation of this phenomenon is still elusive. Essentially, the high risk of MDR-TB in young females could influence the incidence of MDR-TB among children in the future; however, based on Estonia's experience, only one pediatric MDR-TB case has been diagnosed during the recent decade.

Previous reports have found MDR-TB to be correlated with HIV infection [19,48,56]. Our study confirms even an association of HIV infection with XDR-TB. Despite the relatively low HIV prevalence in the study population, the risk of XDR-TB among HIV-infected patients appeared to be three times higher. The study thus implies that any increase in HIV prevalence in the society is particularly cautionary and urges heightened attention to earlier diagnosis of drug-resistant TB and to improvement of measurements to control both HIV and TB infection.

TB has almost always been associated with poor living conditions and poverty. Accordingly to our data, homelessness increased the odds of XDR-TB almost three-fold. Additionally to poor living conditions and malnutrition,

homeless people usually have reduced access to health care services, which prolongs the period of their infectiousness and further increases the risk of transmission of infection among the contacts of homeless TB patients. Once infected owing to the high availability of TB infection in a society, people continuously face the same risk of developing disease later during their lives independently on the methods of TB control [168]. The fact that these considerations are, in the light of the results of the current study, especially linked to XDR-TB makes the TB control perspective epidemiologically frightening.

An association between TB and alcohol abuse, similar to that found in the present study, has been noted also in previous reports [71]. According to our results, alcohol abuse appeared as a risk factor of XDR-TB. A presumptive explanation to this association might be an impact of alcohol consumption on the treatment adherence and final treatment outcome. Several reports have shown that socially disadvantaged patients, such as alcohol abusers and homeless people, are at increased risk of defaulting from treatment and treatment failure [133], thus they have increased risk for developing drug-resistance.

Numerous studies from European countries and the USA emphasize the important role of immigration [48,51,56,77], especially from the countries of the former SU [51,77]. Among the general population recruited for the present study, the risk of MDR-TB and XDR-TB was equally distributed between persons born in Estonia and outside, although of the foreign-born people in the study, almost all originated from the countries of the former SU. Differently, in the age group less than 25 yr, birth outside Estonia was a significant risk factor for MDR-TB. Since all the concerned patients were born in the Russian Federation, one could speculate that migration of people <25 yr of age between neighboring countries of the former SU is also associated with a spread of drug-resistant *M. tuberculosis* strains, in addition to ongoing transmission in the Estonian community. As Estonia is a country with the lowest TB prevalence among the countries the former SU, migration from the Russian Federation, a country with almost twice higher TB prevalence and equal estimated rate of MDR-TB [19], could deteriorate the situation of drug-resistant TB in Estonia due to its geographical position.

High prevalence of TB in prisons and transmission of resistant strains related to overcrowding and inability to isolate resistant cases is internationally well documented [50]. Contrary to these reports, we did not demonstrate an independent association of previous imprisonment with drug-resistant TB, although in 2005, the prevalence of overall TB in Estonian prisons was 544 per 100,000 detainees, i.e. 14.6 times higher than in the general population [33].

The evidence from this study refers to that XDR-TB, a major public health threat, is consistently present thanks to a high proportion of re-treatment cases and may even increase in incidence if the HIV epidemic is left uncontrolled.

6.2. Risk factors of poor treatment outcome and treatment default (II, III)

6.2.1. Treatment outcomes of MDR-TB and XDR-TB (II)

It is known, that interruption of the transmission cycle of drug-resistant TB is possible if the cure rate is higher than 60% [169]. A cure rate of at least 80% is needed to achieve a 10-fold reduction of MDR-TB incidence within 20 years. By the latest WHO Global Tuberculosis Control report [88], the highest MDR-TB success rates have been achieved in the Philippines (73%) and Latvia (71%). In our study, 72.8% of adherent MDR-TB patients and only half of adherent XDR-TB patients achieved a positive treatment outcome, which is bad news for a country with high prevalence of drug-resistance, despite implementing treatment strategies accordingly to WHO-recommended MDR-TB treatment guidelines [41,170]. As a result of implementing the DOTS and DOTS-Plus strategies and quality-assured laboratory services in Estonia since 2001, the MDR-TB prevalence and the proportion of XDR-TB decreased slightly, from 49 XDR-TB cases out of the 281 MDR-TB cases (17.4%) during 2001–2003 to 27 out of 184 cases (14.7%) in 2005–2007 (Estonian TB Registry, unpublished data). Indeed, experiences from many countries affirm that more than just several years of efficient TB control efforts are needed for a country to reduce MDR-TB incidence with appropriate application of the anti-TB chemotherapy [16].

There were at least two factors, which limited achievement of better treatment results in patients with highly drug-resistant TB in our study. Firstly, the overall drug-resistance rate was high, as MDR-TB patients had median resistance to 5.7 TB drugs, whereas XDR-TB patients had median resistance to 6.9 drugs. Based solely on the DST results, it was often impossible to create a treatment regimen with at least 4 effective TB drugs. Secondly, the proportion of defaulters in Estonia was high despite incentives and enablers, such as food and transport reimbursement, were provided daily for all patients in outpatient TB care settings, as well as intensive patient tracing was carried out. Out of all MDR-TB patients, 17.0% interrupted their treatment and the proportion of defaulters among XDR-TB patients was 14.8%.

6.2.2. Risk factors associated with poor treatment outcome in patients with MDR-TB and XDR-TB (II)

In line with the results from prior reports [46], the present study confirms that previous anti-TB treatment significantly increases the risk for poor treatment outcome in MDR-TB. It is well known, that previous TB is the strongest risk factor of being ill with MDR-TB and XDR-TB [56], therefore, special attention has to be paid on improvement treatment adherence of re-treatment cases.

Our present results indicate that positive AFB smear result at the start of treatment is a risk factor of poor treatment outcome both for MDR-TB and XDR-TB. Smear-positive patients often have more advanced disease and longer delay before obtaining medical care. In previous studies, prolonged patient delay has been found to be related with alcohol abuse [171], which was only slightly associated with poor treatment outcome in our study. With better public information, communication, and advocacy, it is possible to impel patients to seek for medical care already when they encounter their first TB symptoms and thereby to shorten the patient delay and to detect the disease in a less advanced phase.

We currently found that poor outcome of XDR-TB treatment is strongly associated with living in an urban area. One speculative explanation of this phenomenon is the huge amount of enticements in an urban environment that may interfere with treatment adherence, despite better accessibility of medical care. Why the same association could not be observed in MDR-TB is possibly because the treatment of XDR-TB is even tougher for the patient due to more numerous medicines taken and more challenging because of the side effects of the treatment. The adherence to treatment of XDR-TB can therefore be more affected or "fragile" as a result. Rationally, the most important tool for improving adherence of patients living in an urban area is improved patient education. Knowing that poor outcome of XDR-TB treatment is strongly associated with urban living, it is easier to concentrate patient education more particularly on this MDR-TB sub-population.

As described in several previous studies [11,19], we found an association of poor MDR-TB treatment outcome with HIV infection. Despite the relatively low HIV prevalence (only 3.8% of MDR-TB patients were HIV-infected), the risk of poor treatment outcome in that particular subpopulation was ten times higher. The raising HIV prevalence is intimidating and attention to early diagnosis of drug-resistant TB and early aggressive MDR-TB treatment should hence be particularly focused on HIV-MDR-TB-co-infected patients. Although not addressed in the present study, combination of TB treatment and antiretroviral therapy has been shown to improve treatment results in co-infected patients [101], thus providing a limited optimism for this vulnerable patient group. The tools allowing to improve treatment outcomes of HIV-infected TB patients could be extensive use of rapid diagnostic methods and immediate start of aggressive anti-TB treatment together with an appropriate antiretroviral therapy.

Several studies emphasize an important role of resistance of *M. tuberculosis* to ofloxacin in poor MDR-TB treatment outcome [46,103]. In our present study, the risk of poor treatment outcome was more than twice higher among those patients, whose bacteria were resistant to ofloxacin. This finding furthermore emphasizes the importance of ofloxacin in MDR-TB treatment regimens and highlights the need for preserving susceptibility to ofloxacin, as well as points out the clinical significance of ofloxacin resistance in the definition of XDR-TB. Contrary to the results of previous studies [91,105], we did not prove an

association between poor treatment outcome and either resistance to injectable second-line TB drugs or resistance to all first-line TB drugs.

In our study population, 53.6% of multidrug-resistant strains belonged to W-Beijing genotype, but presence of this particular *M. tuberculosis* genotype was not associated with poorer treatment outcome. This is contrary to a previous report by Lan *et al.* [172], who documented the W-Beijing genotype as an independent risk factor for treatment failure in TB.

We did not have sufficiently consistent data to analyze the impact of adjuvant surgery and use of linezolid to the treatment outcomes of MDR-TB and XDR-TB patients. Accordingly to some recent studies, both these factors would have a key role in treating drug-resistant TB [94,106–109,111–114]. In Estonia, surgery is used in TB treatment only in limited indications, particularly if adherent patients with drug-resistant TB are still bacteriologically positive after 3-to-6-month treatment and if they have unilateral cavitation only in 1 or 2 lobes. In our cohort, 18 patients underwent surgery. Of them, 11 had MDR-TB/non-XDR-TB and 6 had XDR-TB. Of these patients, 16 cured, thus the treatment success rate was as high as 88.9%. In Estonia, treatment with linezolid is used only for few patients since 2007. Patients with highly drug-resistant TB get linezolid for 2–4 months during the intensive phase of treatment, but this treatment is available only for 3–4 adherent patients per year. The use of linezolid is still limited because of high cost. In particular, linezolid for 1-month treatment costs 50,000 Estonian crowns.

6.2.3. Treatment default rate and causes of treatment default (III)

In our study, 9.4% of patients interrupted their treatment although the treatment was free for anyone, equally accessible for both males and females, and provided only under direct observation, whereas during the outpatient phase of treatment, the food and transport reimbursement were provided daily. In previous studies from Latvia [46] and South Africa [123], the default rates of MDR-TB patients were found similar to those in our present study. In a report from Peru [122], however, the default rate was lower, being 10.0%, but according to a recent report from South Korea, the MDR-TB default rate was more than twice higher than our one, reaching 40.7% [110]. In our cohort, alcohol abuse was the most prevalent reason of treatment default: 77.9% of defaulters were reported of having interrupted their TB treatment because of alcohol abuse.

Treatment default has been found to be linked to the length and complexity of anti-TB treatment, as well as to the fact that most of the patients usually feel much better after the first or second month of treatment [121,173]. In our study, non-MDR-TB patients defaulted from treatment on average 4 months after the start of treatment, whereas MDR-TB patients did so after 8 months. Relying on the data from previous reports [174], one can come to a conclusion that the

majority of defaulted patients, especially those with non-MDR-TB, were probably no more infectious after such a long period of anti-TB treatment. Nowadays, there are still new anti-TB drugs under development that hopefully will shorten the course of TB treatment necessary to achieve abacillation on one hand and will help to reduce the default rate on the other.

During the last year, Estonia has implemented several activities to reduce treatment default and thus to diminish the spread of *M. tuberculosis* infection in the community disseminated by the non-adherent TB patients. First, since 2005, mandatory anti-TB treatment has been put into practice that is executed after court order for infectious repetitive treatment defaulters for 182 days. During the recent years, this mandatory treatment has been applied for approximately 20 TB patients annually (Estonian TB registry; unpublished data), which accounts for about 5% of all detected TB cases per year. Secondly, since 2006, all MDR-TB patients have been provided with all main drugs to relieve the side effects of TB treatment for free. Possibly because of this, side effects of anti-TB treatment were not reported among the major arguments for treatment default in the present study. In numerous previous studies [117,175], side effects of anti-TB treatment have nevertheless been pointed out as independent risk factors of treatment default.

6.2.4. Risk factors associated with treatment default (III)

The present study emphasizes the considerable role of unemployment and alcohol abuse in defaulting from TB treatment. These predictors increased the risk of treatment default threefold. Taken together, our results asserting that socially disadvantaged patients, such as unemployed people, alcohol abusers, and homeless patients, are positioned at an increased risk of defaulting from treatment, are in line with the data from previous studies [118,133]. Thus, to improve the treatment outcomes and thereby make the overall TB epidemiological situation better, special attention has to be paid on improvement of social support to these vulnerable patient populations.

The fact that MDR-TB increases the risk of treatment default is well known. Because the minimum MDR-TB treatment period extends to at least 18 months, the higher MDR-TB patients' default rate is probably related to the longer treatment period. Nevertheless, on TB control's point of view, the high default rate among MDR-TB cases is especially intimidating, because it results in increased spread of multidrug-resistant *M. tuberculosis* infection in the society and will induce new MDR-TB cases, which treatment is less effective, more toxic, and much costlier than the first-line drug-based regimens [2,3] and can further lead to a vicious circle of increased treatment default rate and more vigorous spread of the MDR-TB infection.

In a meta-analysis by Brasil *et al.* [176], the exposure to "difficult-to-access-to-health services" was found one of the strongest risk factor for treatment default. Contrary to this, in our study, treatment default was strongly associated

with living in an urban area. One speculative explanation of this phenomenon is the huge amount of enticements in urban environment that interfere with treatment adherence, despite better accessibility of medical attention itself.

A history of previous treatment default increases the risk of treatment interruption [124,129,130]. Contrary to the previous reports, we did not confirm an association of previous default with recurrent treatment defaults in our study, although 20.6% of defaulters with previous TB had a history of default.

Several studies point out significance of previous imprisonment as a risk factor for TB and drug-resistance related with overcrowding and institutional spread [50,78]. Poor patient adherence to treatment during and after incarceration and high loss to follow-up after release from prison are internationally well known [130,177,178]. This is in concordance with the present finding that treatment default risk was almost twice higher in patients with previous imprisonment. In previous reports, a significant association between HIV infection and poor TB treatment outcome has been described [11,19]. Contrary to the results of previous studies [130,175], we did not prove an association between HIV infection and treatment default.

In the light of our current results, interventions to reduce default from TB treatment should be centered on unemployed patients, alcohol abusers, urban residents, homeless people, and previous prisoners with special supportive attention to MDR-TB patients.

6.2.5. Survival after treatment default and predictors of mortality (III)

It is remarkable that of all defaulters in our study, about one third died after their treatment default. In previous studies on MDR-TB, defaulter's mortality rate was found to vary from 27% in a study from South Africa [123] up to 53% in a report from Peru [122]. The high mortality rate associated with treatment default from TB treatment emphasizes the critical role of prevention of treatment interruption in reducing TB-related mortality.

Unemployment was independently associated with both all-cause and TB-related mortality. In particular, unemployment increased the risk of treatment default threefold and, on the other hand, the all-cause mortality among the unemployed defaulters was eight times higher than among the employed ones. High risk for TB-related death among MDR-TB patients after treatment default also emphasizes a special need for improvement of treatment adherence particularly in the MDR-TB sub-population.

HIV infection has now been acknowledged as one of the strongest risk factors for death after default from TB treatment [148–151]. In our study, HIV infection was close to being significantly associated with all-cause mortality after default. The lack of significance could result from the still low prevalence of HIV infection (only 6.7% of defaulters were HIV-infected), but importantly, the risk of TB-related death in that particular subpopulation was more than fifty

times higher. Accordingly to studies performed earlier [145,148,160,162], in our study, the odds of TB-related death increased among previously treated defaulters and among patients with more advanced disease, i.e. with positive AFB smear results at the start of treatment. These findings indicate that to reduce mortality after treatment default, interventions should be concentrated on patients with multidrug-resistance and HIV-infection, with special attention to unemployed persons and patients with an advanced TB.

7. CONCLUSIONS

1. MDR-TB and XDR-TB share common risk factors, out of which previously treated TB had the strongest association. Predictors for XDR-TB were previous TB treatment, HIV infection, homelessness, and alcohol abuse. Determinants for MDR-TB were previous TB treatment and age ≤ 65 yr. Among the patients ≤ 24 yr of age, multidrug-resistance was associated with female gender and place of birth outside Estonia.

2. In MDR-TB, the overall treatment success rate was 60.4%, being 72.8% among adherent patients. In XDR-TB, these proportions were 42.6% and 50.0%, respectively. The risk factors behind poor treatment outcome in MDR-TB were HIV infection, previous TB treatment, resistance to ofloxacin, and AFB smear-positivity at the start of treatment. Predictors of poor treatment outcome in XDR-TB were urban residence and positive AFB smear at the start of treatment.

3. The overall default rate was 9.4% among all patients with culture-confirmed pulmonary TB and 17.0% among the MDR-TB patients and the most common cause of treatment default was alcohol abuse (77.9%). The independent risk factors for treatment default were alcohol abuse, unemployment, urban residence, and previous imprisonment. The major risk factors for treatment default are thus influenceable ones: to reduce default from TB treatment, interventions should be centered on unemployed patients, alcohol abusers, urban residents, homeless people, and previous prisoners with special regard to MDR-TB patients.

4. Of the defaulters, 29.4% died during the follow-up and unemployment was associated with defaulters' all-cause and TB-related mortality. HIV infection, MDR-TB, previous TB, and sputum smear-positivity at the start of TB treatment were predictors of TB-related mortality. Although preventing defaults from TB treatment is undoubtedly of prime importance, measures to reduce mortality after default should be concentrated on patients with multidrug-resistance and HIV infection, with particular attention to unemployed persons and patients with an advanced TB.

8. REFERENCES

1. World Health Organization. Global Tuberculosis Control 2009. Epidemiology, Strategy, Financing. Geneva, 2009. WHO/HTM/TB/2009.411.
2. Gupta R, Kim JY, Espinal MA, Caudron JM, Pecoul B, Farmer PE, et al. Public health. Responding to market failures in tuberculosis control. Science 2001;293:1049–1051.
3. Loddenkemper R, Sagebiel D, Brendel A. Strategies against multidrug-resistant tuberculosis. Eur Respir J Suppl 2002;36:66s-77s.
4. Migliori GB, Ortmann J, Girardi E, Besozzi G, Lange C, Cirillo DM, et al. Extensively drug-resistant tuberculosis, Italy and Germany. Emerg Infect Dis 2007;13:780–782.
5. Kim HR, Hwang SS, Kim HJ, Lee SM, Yoo CG, Kim YW, et al. Impact of extensive drug resistance on treatment outcomes in non-HIV-infected patients with multidrug-resistant tuberculosis. Clin Infect Dis 2007;45:1290–1295.
6. Chan ED, Iseman MD. Multidrug-resistant and extensively drug-resistant tuberculosis: a review. Curr Opin Infect Dis 2008;21:587–595.
7. Jain A, Dixit P. Multidrug-resistant to extensively drug resistant tuberculosis: what is next? J Biosci 2008;33:605–616.
8. LoBue P. Extensively drug-resistant tuberculosis. Curr Opin Infect Dis 2009;22:167–173.
9. Jassal M, Bishai WR. Extensively drug-resistant tuberculosis. Lancet Infect Dis 2009;9:19–30.
10. Extensively drug-resistant tuberculosis (XDR-TB): recommendations for prevention and control. Wkly Epidemiol Rec 2006;81:430–432.
11. Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 2006;368:1575–1580.
12. Singh JA, Upshur R, Padayatchi N. XDR-TB in South Africa: no time for denial or complacency. PLoS Med 2007;4:e50.
13. Wells CD, Cegielski JP, Nelson LJ, Laserson KF, Holtz TH, Finlay A, et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. J Infect Dis 2007;196 Suppl 1:S86–107.
14. Plan to combat extensively drug-resistant tuberculosis: recommendations of the Federal Tuberculosis Task Force. MMWR Recomm Rep 2009;58:1–43.
15. World Health Organization. Global map and information on XDR-TB. http://www.who.int/tb/challenges/xdr/en/index.html.Accessed on 30 October 2009
16. Emergence of Mycobacterium tuberculosis with extensive resistance to second-line drugs--worldwide, 2000–2004. MMWR Morb Mortal Wkly Rep 2006;55:301–305.
17. Shah NS, Wright A, Bai GH, Barrera L, Boulahbal F, Martin-Casabona N, et al. Worldwide emergence of extensively drug-resistant tuberculosis. Emerg Infect Dis 2007;13:380–387.
18. Toungoussova OS, Bjune G, Caugant DA. Epidemic of tuberculosis in the former Soviet Union: social and biological reasons. Tuberculosis (Edinb) 2006;86:1–10.
19. World Health Organization. Anti-tuberculosis drug resistance in the world. Report No.4. Geneva, 2008. WHO/TB/2008.394.

20. Becerra MC, Bayona J, Freeman J, Farmer PE, Kim JY. Redefining MDR-TB transmission 'hot spots'. Int J Tuberc Lung Dis 2000;4:387–394.
21. Stop TB Partnership and World Health Organization The Global Plan to Stop TB, 2006–2015. Geneva, 2006. WHO/HTM/STB/2006.3.
22. World Health Organization. Global Tuberculosis Control: surveillance, planning, financing: WHO report 2008. Geneva, 2008. WHO/HTM/TB/2008.393.
23. Volmink J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Database Syst Rev 2006:CD003343.
24. Shafer RW, Small PM, Larkin C, Singh SP, Kelly P, Sierra MF, et al. Temporal trends and transmission patterns during the emergence of multidrug-resistant tuberculosis in New York City: a molecular epidemiologic assessment. J Infect Dis 1995;171:170–176.
25. Matteelli A, Migliori GB, Cirillo D, Centis R, Girard E, Raviglion M. Multidrug-resistant and extensively drug-resistant Mycobacterium tuberculosis: epidemiology and control. Expert Rev Anti Infect Ther 2007;5:857–871.
26. Keshavjee S, Gelmanova IY, Farmer PE, Mishustin SP, Strelis AK, Andreev YG, et al. Treatment of extensively drug-resistant tuberculosis in Tomsk, Russia: a retrospective cohort study. Lancet 2008;372:1403–1409.
27. Holtz TH. XDR-TB in South Africa: revised definition. PLoS Med 2007;4:e161.
28. Holtz TH, Cegielski JP. Origin of the term XDR-TB. Eur Respir J 2007;30:396.
29. Extensively drug-resistant tuberculosis--United States, 1993–2006. MMWR Morb Mortal Wkly Rep 2007;56:250–253.
30. Blower SM, Chou T. Modeling the emergence of the 'hot zones': tuberculosis and the amplification dynamics of drug resistance. Nat Med 2004;10:1111–1116.
31. Aaviksoo A, Danilovits M, Hollo V, Kiivet R, Krüüner A, Vink K. Tuberculosis Control Programme 1998–2003. Evaluation ans Summary of Activities. Tallinn, 2004.
32. Viiklepp P. Tuberkuloosihaigestumus Eestis 2007. Tallinn, 2008.
33. Hollo V. Tuberculosis Incidence in Estonia 2005. Tallinn, Estonia, 2007.
34. Bifani PJ, Mathema B, Kurepina NE, Kreiswirth BN. Global dissemination of the Mycobacterium tuberculosis W-Beijing family strains. Trends Microbiol 2002;10:45–52.
35. Glynn JR, Whiteley J, Bifani PJ, Kremer K, van Soolingen D. Worldwide occurrence of Beijing/W strains of Mycobacterium tuberculosis: a systematic review. Emerg Infect Dis 2002;8:843–849.
36. Drobniewski F, Balabanova Y, Nikolayevsky V, Ruddy M, Kuznetzov S, Zakharova S, et al. Drug-resistant tuberculosis, clinical virulence, and the dominance of the Beijing strain family in Russia. Jama 2005;293:2726–2731.
37. Balabanova Ia M, Nikolaevskii VV, Raddi M, Drobnevskii F, Fedorin IM, Erokhin VV, et al. [Preponderance of Mycobacterium tuberculosis strains of the family Beijing and risk factors of their transmission in the Samara Region]. Probl Tuberk Bolezn Legk 2006:31–37.
38. Kruuner A, Hoffner SE, Sillastu H, Danilovits M, Levina K, Svenson SB, et al. Spread of drug-resistant pulmonary tuberculosis in Estonia. J Clin Microbiol 2001;39:3339–3345.
39. Kruuner A, Pehme L, Ghebremichael S, Koivula T, Hoffner SE, Mikelsaar M. Use of molecular techniques to distinguish between treatment failure and exogenous reinfection with Mycobacterium tuberculosis. Clin Infect Dis 2002;35:146–155.

40. UNAIDS/WHO AIDS Epidemic Update: December 2006. http://data.unaids.org/pub/EpiReport/2006/2006_EpiUpdate_en.pdf. Accessed on 30 October 2009.
41. World Health Organization. Guidelines for the programmatic management of drug-resistant Tuberculosis. Geneva, 2006. WHO/HTM/TB/2006.361.
42. Raviglione MC, Uplekar MW. WHO's new Stop TB Strategy. Lancet 2006;367:952–955.
43. Sharma SK, Liu JJ. Progress of DOTS in global tuberculosis control. Lancet 2006;367:951–952.
44. Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. Jama 2000;283:2537–2545.
45. World Health Organization. Guidlines for Establishing DOTS-Plus Pilot Projects for the Management of Multidrug-Resistant Tuberculosis. Geneva, Switzerland, 2000.
46. Leimane V, Riekstina V, Holtz TH, Zarovska E, Skripconoka V, Thorpe LE, et al. Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. Lancet 2005;365:318–326.
47. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis 2009;9:153–161.
48. Casal M, Vaquero M, Rinder H, Tortoli E, Grosset J, Rusch-Gerdes S, et al. A case-control study for multidrug-resistant tuberculosis: risk factors in four European countries. Microb Drug Resist 2005;11:62–67.
49. Clark CM, Li J, Driver CR, Munsiff SS. Risk factors for drug-resistant tuberculosis among non-US-born persons in New York City. Int J Tuberc Lung Dis 2005;9:964–969.
50. Ruddy M, Balabanova Y, Graham C, Fedorin I, Malomanova N, Elisarova E, et al. Rates of drug resistance and risk factor analysis in civilian and prison patients with tuberculosis in Samara Region, Russia. Thorax 2005;60:130–135.
51. Granich RM, Oh P, Lewis B, Porco TC, Flood J. Multidrug resistance among persons with tuberculosis in California, 1994–2003. Jama 2005;293:2732–2739.
52. Choi JC, Lim SY, Suh GY, Chung MP, Kim H, Kwon OJ, et al. Drug resistance rates of Mycobacterium tuberculosis at a private referral center in Korea. J Korean Med Sci 2007;22:677–681.
53. Suarez-Garcia I, Rodriguez-Blanco A, Vidal-Perez JL, Garcia-Viejo MA, Jaras-Hernandez MJ, Lopez O, et al. Risk factors for multidrug-resistant tuberculosis in a tuberculosis unit in Madrid, Spain. Eur J Clin Microbiol Infect Dis 2009;28:325–330.
54. Espinal MA, Laserson K, Camacho M, Fusheng Z, Kim SJ, Tlali RE, et al. Determinants of drug-resistant tuberculosis: analysis of 11 countries. Int J Tuberc Lung Dis 2001;5:887–893.
55. Kimerling ME, Slavuckij A, Chavers S, Peremtin GG, Tonkel T, Sirotkina O, et al. The risk of MDR-TB and polyresistant tuberculosis among the civilian population of Tomsk city, Siberia, 1999. Int J Tuberc Lung Dis 2003;7:866–872.
56. Faustini A, Hall AJ, Perucci CA. Risk factors for multidrug resistant tuberculosis in Europe: a systematic review. Thorax 2006;61:158–163.
57. Pablos-Mendez A, Raviglione MC, Laszlo A, Binkin N, Rieder HL, Bustreo F, et al. Global surveillance for antituberculosis-drug resistance, 1994–1997. World Health Organization-International Union against Tuberculosis and Lung Disease

Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N Engl J Med 1998;338:1641–1649.
58. Lockman S, Kruuner A, Binkin N, Levina K, Wang Y, Danilovitsh M, et al. Clinical outcomes of Estonian patients with primary multidrug-resistant versus drug-susceptible tuberculosis. Clin Infect Dis 2001;32:373–380.
59. Mdivani N, Zangaladze E, Volkova N, Kourbatova E, Jibuti T, Shubladze N, et al. High prevalence of multidrug-resistant tuberculosis in Georgia. Int J Infect Dis 2008;12:635–644.
60. Toungoussova S, Caugant DA, Sandven P, Mariandyshev AO, Bjune G. Drug resistance of Mycobacterium tuberculosis strains isolated from patients with pulmonary tuberculosis in Archangels, Russia. Int J Tuberc Lung Dis 2002;6:406–414.
61. Cox HS, Orozco JD, Male R, Ruesch-Gerdes S, Falzon D, Small I, et al. Multidrug-resistant tuberculosis in central Asia. Emerg Infect Dis 2004;10:865–872.
62. Lomtadze N, Aspindzelashvili R, Janjgava M, Mirtskhulava V, Wright A, Blumberg HM, et al. Prevalence and risk factors for multidrug-resistant tuberculosis in the Republic of Georgia: a population-based study. Int J Tuberc Lung Dis 2009;13:68–73.
63. Suchindran S, Brouwer ES, Van Rie A. Is HIV infection a risk factor for multi-drug resistant tuberculosis? A systematic review. PLoS ONE 2009;4:e5561.
64. Yoshiyama T, Supawitkul S, Kunyanone N, Riengthong D, Yanai H, Abe C, et al. Prevalence of drug-resistant tuberculosis in an HIV endemic area in northern Thailand. Int J Tuberc Lung Dis 2001;5:32–39.
65. Schwoebel V, Decludt B, de Benoist AC, Haeghebaert S, Torrea G, Vincent V, et al. Multidrug resistant tuberculosis in France 1992–4: two case-control studies. BMJ 1998;317:630–631.
66. Conaty SJ, Hayward AC, Story A, Glynn JR, Drobniewski FA, Watson JM. Explaining risk factors for drug-resistant tuberculosis in England and Wales: contribution of primary and secondary drug resistance. Epidemiol Infect 2004;132:1099–1108.
67. Joseph P, Severe P, Ferdinand S, Goh KS, Sola C, Haas DW, et al. Multidrug-resistant tuberculosis at an HIV testing center in Haiti. Aids 2006;20:415–418.
68. Harrow EM, Rangel JM, Arriega JM, Cohen I, Regil Ruiz MI, DeRiemer K, et al. Epidemiology and clinical consequences of drug-resistant tuberculosis in a Guatemalan hospital. Chest 1998;113:1452–1458.
69. Sharma SK, Turaga KK, Balamurugan A, Saha PK, Pandey RM, Jain NK, et al. Clinical and genetic risk factors for the development of multi-drug resistant tuberculosis in non-HIV infected patients at a tertiary care center in India: a case-control study. Infect Genet Evol 2003;3:183–188.
70. Primary multidrug-resistant tuberculosis--Ivanovo Oblast, Russia, 1999. MMWR Morb Mortal Wkly Rep 1999;48:661–664.
71. Tekkel M, Rahu M, Loit HM, Baburin A. Risk factors for pulmonary tuberculosis in Estonia. Int J Tuberc Lung Dis 2002;6:887–894.
72. Lienhardt C, Fielding K, Sillah JS, Bah B, Gustafson P, Warndorff D, et al. Investigation of the risk factors for tuberculosis: a case-control study in three countries in West Africa. Int J Epidemiol 2005;34:914–923.
73. Moore M, Onorato IM, McCray E, Castro KG. Trends in drug-resistant tuberculosis in the United States, 1993–1996. Jama 1997;278:833–837.

74. Granich RM, Moore M, Binkin NJ, McRay E. Drug-resistant tuberculosis in foreign-born persons from Mexico, the Philippines, and Vietnam-United States, 1993–1997. Int J Tuberc Lung Dis 2001;5:53–58.
75. Migliori GB, Fattorini L, Vaccarino P, Besozzi G, Saltini C, Orefici G, et al. Prevalence of resistance to anti-tuberculosis drugs: results of the 1998/99 national survey in Italy. Int J Tuberc Lung Dis 2002;6:32–38.
76. Moniruzzaman A, Elwood RK, Schulzer M, FitzGerald JM. A population-based study of risk factors for drug-resistant TB in British Columbia. Int J Tuberc Lung Dis 2006;10:631–638.
77. Falzon D, Infuso A, Ait-Belghiti F. In the European Union, TB patients from former Soviet countries have a high risk of multidrug resistance. Int J Tuberc Lung Dis 2006;10:954–958.
78. Coker R, McKee M, Atun R, Dimitrova B, Dodonova E, Kuznetsov S, et al. Risk factors for pulmonary tuberculosis in Russia: case-control study. BMJ 2006;332:85–87.
79. Jugheli L, Rigouts L, Shamputa IC, Bram de Rijk W, Portaels F. High levels of resistance to second-line anti-tuberculosis drugs among prisoners with pulmonary tuberculosis in Georgia. Int J Tuberc Lung Dis 2008;12:561–566.
80. Lobacheva T, Asikainen T, Giesecke J. Risk factors for developing tuberculosis in remand prisons in St. Petersburg, Russia - a case-control study. Eur J Epidemiol 2007;22:121–127.
81. Jeon CY, Hwang SH, Min JH, Prevots DR, Goldfeder LC, Lee H, et al. Extensively drug-resistant tuberculosis in South Korea: risk factors and treatment outcomes among patients at a tertiary referral hospital. Clin Infect Dis 2008;46:42–49.
82. Shah NS, Pratt R, Armstrong L, Robison V, Castro KG, Cegielski JP. Extensively drug-resistant tuberculosis in the United States, 1993–2007. Jama 2008;300:2153–2160.
83. Vilarica AS, Gomes C, Pina J. Comparative analysis of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis – Epidemiology and predictive factors. Rev Port Pneumol 2008;14:829–842.
84. Kolappan C, Subramani R, Karunakaran K, Narayanan PR. Mortality of tuberculosis patients in Chennai, India. Bull World Health Organ 2006;84:555–560.
85. Pablos-Mendez A, Knirsch CA, Barr RG, Lerner BH, Frieden TR. Nonadherence in tuberculosis treatment: predictors and consequences in New York City. Am J Med 1997;102:164–170.
86. Mitnick C, Bayona J, Palacios E, Shin S, Furin J, Alcantara F, et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. N Engl J Med 2003;348:119–128.
87. Shin SS, Pasechnikov AD, Gelmanova IY, Peremitin GG, Strelis AK, Mishustin S, et al. Treatment outcomes in an integrated civilian and prison MDR-TB treatment program in Russia. Int J Tuberc Lung Dis 2006;10:402–408.
88. World Health Organization. WHO Report 2009. Global Tuberculosis Control. Epidemiology, Strategy, Financing.Geneva, Switzerland, 2009.
89. Blaas SH, Mutterlein R, Weig J, Neher A, Salzberger B, Lehn N, et al. Extensively drug resistant tuberculosis in a high income country: a report of four unrelated cases. BMC Infect Dis 2008;8:60.

90. Jeon DS, Kim DH, Kang HS, Hwang SH, Min JH, Kim JH, et al. Survival and predictors of outcomes in non-HIV-infected patients with extensively drug-resistant tuberculosis. Int J Tuberc Lung Dis 2009;13:594–600.
91. Migliori GB, Besozzi G, Girardi E, Kliiman K, Lange C, Toungoussova OS, et al. Clinical and operational value of the extensively drug-resistant tuberculosis definition. Eur Respir J 2007;30:623–626.
92. Mitnick CD, Shin SS, Seung KJ, Rich ML, Atwood SS, Furin JJ, et al. Comprehensive treatment of extensively drug-resistant tuberculosis. N Engl J Med 2008;359:563–574.
93. Sotgiu G, Ferrara G, Matteelli A, Richardson MD, Centis R, Ruesch-Gerdes S, et al. Epidemiology and clinical management of XDR-TB: a systematic review by TBNET. Eur Respir J 2009;33:871–881.
94. Kwon YS, Kim YH, Suh GY, Chung MP, Kim H, Kwon OJ, et al. Treatment outcomes for HIV-uninfected patients with multidrug-resistant and extensively drug-resistant tuberculosis. Clin Infect Dis 2008;47:496–502.
95. Chiang CY, Yew WW. Multidrug-resistant and extensively drug-resistant tuberculosis. Int J Tuberc Lung Dis 2009;13:304–311.
96. Hollo V. Tuberculosis Incidence in Estonia 2006. Tallinn, Estonia, 2008.
97. Kawai V, Soto G, Gilman RH, Bautista CT, Caviedes L, Huaroto L, et al. Tuberculosis mortality, drug resistance, and infectiousness in patients with and without HIV infection in Peru. Am J Trop Med Hyg 2006;75:1027–1033.
98. Coker RJ. Review: multidrug-resistant tuberculosis: public health challenges. Trop Med Int Health 2004;9:25–40.
99. Drobniewski F, Eltringham I, Graham C, Magee JG, Smith EG, Watt B. A national study of clinical and laboratory factors affecting the survival of patients with multiple drug resistant tuberculosis in the UK. Thorax 2002;57:810–816.
100. Jack C, Lalloo U, Karim QA, Karim SA, El-Sadr W, Cassol S, et al. A pilot study of once-daily antiretroviral therapy integrated with tuberculosis directly observed therapy in a resource-limited setting. J Acquir Immune Defic Syndr 2004;36:929–934.
101. Dheda K, Lampe FC, Johnson MA, Lipman MC. Outcome of HIV-associated tuberculosis in the era of highly active antiretroviral therapy. J Infect Dis 2004;190:1670–1676.
102. Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. Lancet 2002;359:2059–2064.
103. Migliori GB, Lange C, Girardi E, Centis R, Besozzi G, Kliiman K, et al. Fluoro-quinolones: are they essential to treat multidrug-resistant tuberculosis? Eur Respir J 2008;31:904–905.
104. Chiang CY, Enarson DA, Yu MC, Bai KJ, Huang RM, Hsu CJ, et al. Outcome of pulmonary multidrug-resistant tuberculosis: a 6-yr follow-up study. Eur Respir J 2006;28:980–985.
105. Migliori GB, Lange C, Centis R, Sotgiu G, Mutterlein R, Hoffmann H, et al. Resistance to second-line injectables and treatment outcomes in multidrug-resistant and extensively drug-resistant tuberculosis cases. Eur Respir J 2008; 31:1155–1159.
106. von der Lippe B, Sandven P, Brubakk O. Efficacy and safety of linezolid in multidrug resistant tuberculosis (MDR-TB)--a report of ten cases. J Infect 2006;52:92–96.

107. Yew WW, Chau CH, Wen KH. Linezolid in the treatment of 'difficult' multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2008;12:345–346.
108. Condos R, Hadgiangelis N, Leibert E, Jacquette G, Harkin T, Rom WN. Case series report of a linezolid-containing regimen for extensively drug-resistant tuberculosis. Chest 2008;134:187–192.
109. Torun T, Tahaoglu K, Ozmen I, Sevim T, Atac G, Kir A, et al. The role of surgery and fluoroquinolones in the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2007;11:979–985.
110. Kim DH, Kim HJ, Park SK, Kong SJ, Kim YS, Kim TH, et al. Treatment Outcomes and Long-term Survival in Patients with Extensively Drug-resistant Tuberculosis. Am J Respir Crit Care Med 2008.
111. Chan ED, Laurel V, Strand MJ, Chan JF, Huynh ML, Goble M, et al. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2004;169:1103–1109.
112. Somocurcio JG, Sotomayor A, Shin S, Portilla S, Valcarcel M, Guerra D, et al. Surgery for patients with drug-resistant tuberculosis: report of 121 cases receiving community-based treatment in Lima, Peru. Thorax 2007;62:416–421.
113. Pomerantz M, Madsen L, Goble M, Iseman M. Surgical management of resistant mycobacterial tuberculosis and other mycobacterial pulmonary infections. Ann Thorac Surg 1991;52:1108–1111; discussion 1112.
114. Kir A, Tahaoglu K, Okur E, Hatipoglu T. Role of surgery in multi-drug-resistant tuberculosis: results of 27 cases. Eur J Cardiothorac Surg 1997;12:531–534.
115. Pomerantz BJ, Cleveland JC, Jr., Olson HK, Pomerantz M. Pulmonary resection for multi-drug resistant tuberculosis. J Thorac Cardiovasc Surg 2001;121:448–453.
116. Demissie M, Kebede D. Defaulting from tuberculosis treatment at the Addis Abeba Tuberculosis Centre and factors associated with it. Ethiop Med J 1994;32:97–106.
117. Tekle B, Mariam DH, Ali A. Defaulting from DOTS and its determinants in three districts of Arsi Zone in Ethiopia. Int J Tuberc Lung Dis 2002;6:573–579.
118. Hasker E, Khodjikhanov M, Usarova S, Asamidinov U, Yuldashova U, van der Werf MJ, et al. Default from tuberculosis treatment in Tashkent, Uzbekistan; who are these defaulters and why do they default? BMC Infect Dis 2008;8:97.
119. Santha T, Garg R, Frieden TR, Chandrasekaran V, Subramani R, Gopi PG, et al. Risk factors associated with default, failure and death among tuberculosis patients treated in a DOTS programme in Tiruvallur District, South India, 2000. Int J Tuberc Lung Dis 2002;6:780–788.
120. Gelmanova IY, Keshavjee S, Golubchikova VT, Berezina VI, Strelis AK, Yanova GV, et al. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance. Bull World Health Organ 2007;85:703–711.
121. Kruk ME, Schwalbe NR, Aguiar CA. Timing of default from tuberculosis treatment: a systematic review. Trop Med Int Health 2008;13:703–712.
122. Franke MF, Appleton SC, Bayona J, Arteaga F, Palacios E, Llaro K, et al. Risk factors and mortality associated with default from multidrug-resistant tuberculosis treatment. Clin Infect Dis 2008;46:1844–1851.
123. Holtz TH, Lancaster J, Laserson KF, Wells CD, Thorpe L, Weyer K. Risk factors associated with default from multidrug-resistant tuberculosis treatment, South Africa, 1999–2001. Int J Tuberc Lung Dis 2006;10:649–655.

124. Chan-Yeung M, Noertjojo K, Leung CC, Chan SL, Tam CM. Prevalence and predictors of default from tuberculosis treatment in Hong Kong. Hong Kong Med J 2003;9:263–268.
125. Botha E, Den Boon S, Verver S, Dunbar R, Lawrence KA, Bosman M, et al. Initial default from tuberculosis treatment: how often does it happen and what are the reasons? Int J Tuberc Lung Dis 2008;12:820–823.
126. Buu TN, Lonnroth K, Quy HT. Initial defaulting in the National Tuberculosis Programme in Ho Chi Minh City, Vietnam: a survey of extent, reasons and alternative actions taken following default. Int J Tuberc Lung Dis 2003;7:735–741.
127. Munro SA, Lewin SA, Smith HJ, Engel ME, Fretheim A, Volmink J. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Med 2007;4:e238.
128. Brasil PE, Braga JU. Meta-analysis of factors related to health services that predict treatment default by tuberculosis patients. Cad Saude Publica 2008;24 Suppl 4:s485–502.
129. Chang KC, Leung CC, Tam CM. Risk factors for defaulting from anti-tuberculosis treatment under directly observed treatment in Hong Kong. Int J Tuberc Lung Dis 2004;8:1492–1498.
130. Caceres Fde M, Orozco LC. [Incidence of and factors for non-compliance to antituberculous treatment]. Biomedica 2007;27:498–504.
131. Rakotonirina el CJ, Ravaoarisoa L, Randriatsarafara FM, Rakotomanga Jde D, Robert A. [Factors associated with tuberculosis treatment default in Antananarivo city, Madagascar]. Sante Publique 2009;21:139–146.
132. de Albuquerque Mde F, Ximenes RA, Lucena-Silva N, de Souza WV, Dantas AT, Dantas OM, et al. Factors associated with treatment failure, dropout, and death in a cohort of tuberculosis patients in Recife, Pernambuco State, Brazil. Cad Saude Publica 2007;23:1573–1582.
133. Jakubowiak WM, Bogorodskaya EM, Borisov SE, Danilova ID, Kourbatova EV. Risk factors associated with default among new pulmonary TB patients and social support in six Russian regions. Int J Tuberc Lung Dis 2007;11:46–53.
134. Cayla JA, Caminero JA, Rey R, Lara N, Valles X, Galdos-Tanguis H. Current status of treatment completion and fatality among tuberculosis patients in Spain. Int J Tuberc Lung Dis 2004;8:458–464.
135. Diel R, Niemann S. Outcome of tuberculosis treatment in Hamburg: a survey, 1997–2001. Int J Tuberc Lung Dis 2003;7:124–131.
136. Mitike G, Kebede D, Yeneneh H. HIV infection and antituberculosis drug resistance among pulmonary tuberculosis patients in Harar Tuberculosis Centre, Ethiopia. East Afr Med J 1997;74:154–157.
137. Connolly C, Davies GR, Wilkinson D. Who fails to complete tuberculosis treatment? Temporal trends and risk factors for treatment interruption in a community-based directly observed therapy programme in a rural district of South Africa. Int J Tuberc Lung Dis 1999;3:1081–1087.
138. Liam CK, Lim KH, Wong CM, Tang BG. Attitudes and knowledge of newly diagnosed tuberculosis patients regarding the disease, and factors affecting treatment compliance. Int J Tuberc Lung Dis 1999;3:300–309.
139. Kapella BK, Anuwatnonthakate A, Komsakorn S, Moolphate S, Charusuntonsri P, Limsomboon P, et al. Directly observed treatment is associated with reduced default among foreign tuberculosis patients in Thailand. Int J Tuberc Lung Dis 2009;13:232–237.

140. Liefooghe R, Suetens C, Meulemans H, Moran MB, De Muynck A. A randomised trial of the impact of counselling on treatment adherence of tuberculosis patients in Sialkot, Pakistan. Int J Tuberc Lung Dis 1999;3:1073–1080.
141. Shean KP, Willcox PA, Siwendu SN, Laserson KF, Gross L, Kammerer S, et al. Treatment outcome and follow-up of multidrug-resistant tuberculosis patients, West Coast/Winelands, South Africa, 1992–2002. Int J Tuberc Lung Dis 2008;12:1182–1189.
142. Sai Babu B, Satyanarayana AV, Venkateshwaralu G, Ramakrishna U, Vikram P, Sahu S, et al. Initial default among diagnosed sputum smear-positive pulmonary tuberculosis patients in Andhra Pradesh, India. Int J Tuberc Lung Dis 2008;12:1055–1058.
143. Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh CR, Jr. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. N Engl J Med 1993;328:527–532.
144. Frieden TR, Sterling T, Pablos-Mendez A, Kilburn JO, Cauthen GM, Dooley SW. The emergence of drug-resistant tuberculosis in New York City. N Engl J Med 1993;328:521–526.
145. Mathew TA, Ovsyanikova TN, Shin SS, Gelmanova I, Balbuena DA, Atwood S, et al. Causes of death during tuberculosis treatment in Tomsk Oblast, Russia. Int J Tuberc Lung Dis 2006;10:857–863.
146. Lefebvre N, Falzon D. Risk factors for death among tuberculosis cases: analysis of European surveillance data. Eur Respir J 2008;31:1256–1260.
147. Low S, Ang LW, Cutter J, James L, Chee CB, Wang YT, et al. Mortality among tuberculosis patients on treatment in Singapore. Int J Tuberc Lung Dis 2009;13:328–334.
148. Lawn SD, Acheampong JW. Pulmonary tuberculosis in adults: factors associated with mortality at a Ghanaian teaching hospital. West Afr J Med 1999;18:270–274.
149. Sterling TR, Zhao Z, Khan A, Chaisson RE, Schluger N, Mangura B, et al. Mortality in a large tuberculosis treatment trial: modifiable and non-modifiable risk factors. Int J Tuberc Lung Dis 2006;10:542–549.
150. Nunn P, Brindle R, Carpenter L, Odhiambo J, Wasunna K, Newnham R, et al. Cohort study of human immunodeficiency virus infection in patients with tuberculosis in Nairobi, Kenya. Analysis of early (6-month) mortality. Am Rev Respir Dis 1992;146:849–854.
151. Domingos MP, Caiaffa WT, Colosimo EA. Mortality, TB/HIV co-infection, and treatment dropout: predictors of tuberculosis prognosis in Recife, Pernambuco State, Brazil. Cad Saude Publica 2008;24:887–896.
152. Manosuthi W, Chottanapand S, Thongyen S, Chaovavanich A, Sungkanuparph S. Survival rate and risk factors of mortality among HIV/tuberculosis-coinfected patients with and without antiretroviral therapy. J Acquir Immune Defic Syndr 2006;43:42–46.
153. Kolappan C, Subramani R, Kumaraswami V, Santha T, Narayanan PR. Excess mortality and risk factors for mortality among a cohort of TB patients from rural south India. Int J Tuberc Lung Dis 2008;12:81–86.
154. Vasankari T, Holmstrom P, Ollgren J, Liippo K, Kokki M, Ruutu P. Risk factors for poor tuberculosis treatment outcome in Finland: a cohort study. BMC Public Health 2007;7:291.
155. Barnes PF, Leedom JM, Chan LS, Wong SF, Shah J, Vachon LA, et al. Predictors of short-term prognosis in patients with pulmonary tuberculosis. J Infect Dis 1988;158:366–371.

156. Bustamante-Montes LP, Escobar-Mesa A, Borja-Aburto VH, Gomez-Munoz A, Becerra-Posada F. Predictors of death from pulmonary tuberculosis: the case of Veracruz, Mexico. Int J Tuberc Lung Dis 2000;4:208–215.
157. Zafran N, Heldal E, Pavlovic S, Vuckovic D, Boe J. Why do our patients die of active tuberculosis in the era of effective therapy? Tuber Lung Dis 1994;75:329–333.
158. Lubart E, Lidgi M, Leibovitz A, Rabinovitz C, Segal R. Mortality of patients hospitalized for active tuberculosis in Israel. Isr Med Assoc J 2007;9:870–873.
159. Kourbatova EV, Borodulin BE, Borodulina EA, del Rio C, Blumberg HM, Leonard MK, Jr. Risk factors for mortality among adult patients with newly diagnosed tuberculosis in Samara, Russia. Int J Tuberc Lung Dis 2006;10:1224–1230.
160. Vasantha M, Gopi PG, Subramani R. Survival of tuberculosis patients treated under DOTS in a rural Tuberculosis Unit (TU), south India. Indian J Tuberc 2008;55:64–69.
161. Pelaquin MH, Souza e Silva R, Ribeiro SA. Factors associated with death by tuberculosis in the eastern part of Sao Paulo city, 2001. J Bras Pneumol 2007;33:311–317.
162. Dewan PK, Arguin PM, Kiryanova H, Kondroshova NV, Khorosheva TM, Laserson K, et al. Risk factors for death during tuberculosis treatment in Orel, Russia. Int J Tuberc Lung Dis 2004;8:598–602.
163. Chiang CY, Lee JJ, Yu MC, Enarson DA, Lin TP, Luh KT. Tuberculosis outcomes in Taipei: factors associated with treatment interruption for 2 months and death. Int J Tuberc Lung Dis 2009;13:105–111.
164. Laserson KF, Thorpe LE, Leimane V, Weyer K, Mitnick CD, Riekstina V, et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2005;9:640–645.
165. Laszlo A, Rahman M, Espinal M, Raviglione M. Quality assurance programme for drug susceptibility testing of Mycobacterium tuberculosis in the WHO/IUATLD Supranational Reference Laboratory Network: five rounds of proficiency testing, 1994–1998. Int J Tuberc Lung Dis 2002;6:748–756.
166. Kamerbeek J, Schouls L, Kolk A, van Agterveld M, van Soolingen D, Kuijper S, et al. Simultaneous detection and strain differentiation of Mycobacterium tuberculosis for diagnosis and epidemiology. J Clin Microbiol 1997;35:907–914.
167. Brudey K, Driscoll JR, Rigouts L, Prodinger WM, Gori A, Al-Hajoj SA, et al. Mycobacterium tuberculosis complex genetic diversity: mining the fourth international spoligotyping database (SpolDB4) for classification, population genetics and epidemiology. BMC Microbiol 2006;6:23.
168. Haro AS. Cohort approach in tuberculosis surveillance: comparison of the situation in Sweden and Finland. Tuber Lung Dis 1994;75:271–282.
169. Dye C, Williams BG. Criteria for the control of drug-resistant tuberculosis. Proc Natl Acad Sci U S A 2000;97:8180–8185.
170. Mukherjee JS, Rich ML, Socci AR, Joseph JK, Viru FA, Shin SS, et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. Lancet 2004;363:474–481.
171. Kiwuwa MS, Charles K, Harriet MK. Patient and health service delay in pulmonary tuberculosis patients attending a referral hospital: a cross-sectional study. BMC Public Health 2005;5:122.

172. Lan NT, Lien HT, Tung le B, Borgdorff MW, Kremer K, van Soolingen D. Mycobacterium tuberculosis Beijing genotype and risk for treatment failure and relapse, Vietnam. Emerg Infect Dis 2003;9:1633–1635.
173. Bam TS, Gunneberg C, Chamroonsawasdi K, Bam DS, Aalberg O, Kasland O, et al. Factors affecting patient adherence to DOTS in urban Kathmandu, Nepal. Int J Tuberc Lung Dis 2006;10:270–276.
174. Holtz TH, Sternberg M, Kammerer S, Laserson KF, Riekstina V, Zarovska E, et al. Time to sputum culture conversion in multidrug-resistant tuberculosis: predictors and relationship to treatment outcome. Ann Intern Med 2006;144:650–659.
175. Rabahi MF, Rodrigues AB, Queiroz de Mello F, de Almeida Netto JC, Kritski AL. Noncompliance with tuberculosis treatment by patients at a tuberculosis and AIDS reference hospital in midwestern Brazil. Braz J Infect Dis 2002;6:63–73.
176. do Brasil PE, Braga JU. Meta-analysis of factors related to health services that predict treatment default by tuberculosis patients. Cad Saude Publica 2008;24 Suppl 4:s485–502.
177. Pfyffer GE, Strassle A, van Gorkum T, Portaels F, Rigouts L, Mathieu C, et al. Multidrug-resistant tuberculosis in prison inmates, Azerbaijan. Emerg Infect Dis 2001;7:855–861.
178. Coninx R, Maher D, Reyes H, Grzemska M. Tuberculosis in prisons in countries with high prevalence. BMJ 2000;320:440–442.

SUMMARY IN ESTONIAN

Ravimresistentne tuberkuloos Eestis: riskifaktorid ja negatiivse ravitulemuse riskitegurid

Maailma Terviseorganisatsiooni (MTO) hinnangul haigestus 2007. aastal üle kogu maailma esmakordselt tuberkuloosi (TB) 9,27 miljonit inimest, kusjuures 15% neist olid tõenäoliselt HIV-infitseeritud ning TB-st tingitud surmajuhtumite arv oli 1,76 miljonit [1]. Lisaks kõrgele TB-haigestumusele on viimastel aastatel kogu maailmas muutunud tõsiseks probleemiks multiravimresistentne TB (MDR-TB), mille korral haigustekitaja *Mycobacterium tuberculosis* on resistentne vähemalt kahele TB põhipreparaadile, isoniasiidile ja rifampitsiinile. MDR-TB ravis kasutatakse nn teise rea TB-ravimeid, mis võrreldes nn esimese rea TB ravimitega on vähemefektiivsed, põhjustavad rohkem kõrvaltoimeid ja on oluliselt kallimad [2]. Seetõttu on ka MDR-TB haigete ravitulemused võrreldes ravimtundliku TB ravitulemustega oluliselt halvemad [3]. 2006. aastal võeti kasutusele mõiste eriti resistentne TB (XDR-TB), mille puhul on tegemist MDR-TB juhuga, kus lisandub haigustekitaja resistentsus fluorokinoloonile ja vähemalt ühele teise rea süstitavale TB-vastasele ravimile [4–9]. XDR-TB haigete ravitulemused on olnud võrreldes MDR-TB haigetega veelgi halvemad [4,5,89], eriti kombinatsioonis HIV-infektsiooniga [11]. MTO hinnangul lisandub kogu maailmas aastas 500 000 uut MDR-TB ja 40 000 uut XDR-TB juhtu. *M. tuberculosis'*e ravimresistentsuse kujunemine on seotud kas meditsiinipoolsete vigadega (mittestandardiseeritud raviskeemide kasutamine, ravimitega varustamise ebaregulaarsus ja otseselt kontrollitava ravi mittekasutamine) või patsiendipoolsete põhjustega (ebaregulaarne ja mitte kõigi määratud ravimite võtmine) [24]. Ravimresistentsus võib olla esmane, mille korral patsient nakatub ravimresistentse bakteriga või omandatud, mille korral ravimresistentsus kujuneb välja esmaselt ravimtundliku haigustekitajaga patsiendil.

MTO poolt TB raviks soovitatav DOTS-strateegia koosneb 5 komponendist: 1) valitsuse toetus tuberkuloositõrje programmile, 2) TB diagnostika mikrobioloogiliste meetoditega, 3) standardiseeritud otseselt kontrollitud raviskeemide kasutamine, 4) regulaarne ravimitega varustamine ja 5) ühtne registreerimis- ja kontrollsüsteem. DOTS-strateegia laialdane kasutamine on oluliselt parandanud TB situatsiooni kogu maailmas [42,43]. MTO poolt soovitatav ravirežiim MDR-TB haigete raviks koosneb vähemalt neljast (kuni üheksast) TB-vastasest ravimist maksimaalsetes lubatud annustes vähemalt 18 kuni 24 kuu jooksul [45] ning vastava raviga on põhimõtteliselt saavutatav enamiku MDR-TB haigete paranemine [25,46].

2005. aastal kogu maailmas DOTS-programmi raames ravi alustanud uutest bakterioskoopiliselt positiivsetest kopsu-TB-haigetest paranes 84,7% ning retsidiivjuhtude hulgas oli positiivse ravitulemuse osakaal 71,0%. Kogu maailmas on jätkuvalt probleemiks ravikatkestajate suhteliselt suur osakaal, see ulatus vastavates kohortides 5,4% ja 12,0%-ni. TB ravi ebaõnnestumine ja ravi

katkestamine põhjustab edasist TB-nakkuse levikut, ravimresistentsuse kujunemist, taashaigestumist TB-i ning TB põhjustatud surmasid [84,85]. 2009. aasta MTO tuberkuloosi globaalse kontrolli raportis [22] on parimad MDR-TB haigete ravitulemused saavutatud Filipiinidel ja Lätis, kus paranes vastavalt 73% ja 71% haigetest. Madalaimad ravitulemused olid Rumeenias ja Marokos, kus paranes üksnes 38% ja 25% MDR-TB haigetest. XDR-TB haigete raviskeemide koostamine on sageli komplitseeritud, kuna hetkel kasutada olevate TB vastaste ravimitega on neile sageli võimatu koostada raviskeemi, mis sisaldaks vähemalt nelja toimivat ravimit. XDR-TB haigete positiivne ravitulemus madala HIV levikuga riikides on ulatunud 20%-st Lõuna Koreas [90] 40%-ni Eesti, Saksamaa, Itaalia ja Vene Föderatsiooni ühisuuringus [91]. Parimad XDR-TB haigete ravitulemused on saavutatud Peruus, kus 60,4% HIV-negatiivsetest XDR-TB juhtudest ning 66,3% MDR-TB juhtudest paranes ning surma risk ei olnud XDR-TB ja MDR-TB haigetel erinev [92]. Hiljutiste uuringute põhjal võib järeldada, et ka XDR-TB on ravitav kasutades MDR-TB ravistrateegiaid, vältides diagnoosi hilinemist ning alustades maksimaalselt agressiivset medikamentoosset ravi ja vajadusel kasutades ka kirurgilist ravi [26,93–95].

Nõukogude Liidu lagunemise järel Eestis toimunud sotsiaal-majanduslike muutuste tõttu tõusis TB-haigestumus oluliselt. TB esmashaigestumus kahekordistus 1990ndatel ning 1997. aastal diagnoositi Eestis 51 uut TB haigusjuhtu 100 000 elaniku kohta [31]. Alates 2000. aastast on Eestis rakendatud MTO soovitatud DOTS-strateegiat ja augustis 2001 alustati DOTS-Plus projektiga MDR-TB haigete raviks. Tänu riiklikule TB tõrje programmile ja kopsuarstide efektiivsele tööle on viimastel aastatel TB haigestumus langenud 8% aastas ja MDR-TB haigete suhtarv uute haigusjuhtude hulgas ei ole tõusnud. Samas püsib MDR-TB ja XDR-TB haigete suhtarv jätkuvalt kõrgena [19]. 2005. aastal diagnoositi MDR-TB 14,1% kõikidest testitud uutest TB juhtudest ning 48,1% varasemalt TB-vastast ravi saanud juhtudest. Kõikidest diagnoositud MDR-TB juhtudest 20,6% olid XDR-TB juhud (vastavalt 11,9% uutest ja 34,6% varasemalt ravitud juhtudest) [33]. Eestis on tõsiseks kaasnevaks probleemiks HIV-infektsiooni laialdane levik. 2008. aasta lõpuks oli Eestis 6909 inimesel diagnoositud HIV-infektsioon ning kõikidest samal aastal diagnoositud TB-juhtudest olid 9,4% HIV-infitseeritud. Eestis on TB ravi üheks peamiseks probleemiks suur ravikatkestajate osakaal. 2005. aastal ravi alustanud TB-haigetest paranes 83,6% mitte-MDR-TB juhtudest ja 55,7% MDR-TB juhtudest, kuid ravi katkestas 10,7% mitte-MDR-TB haigetest ja 21,5% MDR-TB haigetest [33,96].

UURINGU EESMÄRGID

Analüüsimaks kõrget MDR-TB ja XDR-TB suhtarvu põhjustavaid tegureid Eestis kaasati populatsioonipõhisesse retrospektiivsesse uuringusse kõik Eestis

ajavahemikul jaanuar 2003 kuni detsember 2005 diagnoositud bakterioloogiliselt tõendatud kopsu-TB patsiendid.

Töö eesmärgid olid:
1) analüüsida MDR-TB ja XDR-TB riskifaktoreid;
2) hinnata TB-haigete ravi efektiivsust ning teha kindlaks ravi ebaõnnestumise riskitegurid MDR-TB ja XDR-TB haigetel;
3) selgitada välja TB-haigete ravi katkestamise põhjused ning selgitada välja ravi katkestamise riskifaktorid;
4) hinnata TB-haigete ravikatkestamisega seotud suremust ning leida sellega seotud riskitegurid.

MATERJAL JA MEETODID

MDR-TB ja XDR-TB riskifaktorid (I)

Uuringusse kaasati kõik bakterioloogiliselt kinnitatud kopsu-TB patsiendid, kelle haigus diagnoositi ajavahemikus 1. jaanuarist 2003 kuni 31. detsembrini 2005. Uuringust jäeti välja nn kroonilise TB patsiendid (patsiendid, kes olid jätkuvalt bakterieritajad pärast korduva TB ravikuuri lõpetamist). Patsiendid jaotati 3 gruppi: 1) patsiendid mitte-MDR-TB-ga, 2) patsiendid MDR-TB, kuid mitte XDR-TB-ga ja 3) patsiendid XDR-TB-ga.

Halva ravitulemuse ja ravi katkestamise riskitegurid (II, III)

Uuringusse kaasati kõik bakterioloogiliselt kinnitatud kopsu-TB patsiendid, kelle haigus diagnoositi ajavahemikus 1. jaanuarist 2003 kuni 31. detsembrini 2005 ja kes seejärel alustasid TB-vastast ravi ning kellel oli teada ravi tulemus (patsiendid, kes paranesid, lõpetasid ravikuuri, surid või kelle ravi oli ebaefektiivne). Uuritavate hulgast jäeti välja patsiendid, kellel ei olnud lõplikku ravitulemust (jätkasid ravi või lahkusid Eestist) ning nn kroonilise TB-ga patsiendid.

Halva ravitulemuse riskitegurite uuringus jaotati patsiendid sarnaselt MDR-TB ja XDR-TB riskitegurite uuringuga kolme gruppi. Ravikatkestajate uuringus jaotati patsiendid 2 gruppi: 1) ravi katkestajad ja 2) ravi mittekatkestajad.

Definitsioonid

Kõik patsiendid klassifitseeriti uuteks TB juhtudeks (haigusjuhud, mille puhul ei oldud kunagi TB ravi saanud või oldi saanud seda < 1 kuu vältel) või retsidiivjuhtudeks (patsiendid, kes olid saanud eelnevalt TB ravi ≥ 1 kuu vältel kas esimese või teise rea TB ravimitega).

MDR-TB juhud olid haigusjuhud, mille haigustekitaja oli samaaegselt resistentne nii isoniasiidile kui rifampitsiinile ja XDR-TB juhud olid MDR-TB juhud, mille haigustekitaja oli lisaks resistentne fluorokinoloonile ja vähemalt ühele süstitavale teise rea preparaadile (kapreomütsiinile, kanamütsiinile või amikatsiinile).

Ravitulemuste definitsioonid olid järgnevad. Mitte-MDR-TB juhtude hulgas oli ravitulemusega "paranenud" patsient, kes eelnevalt oli bakterieritaja ning kes lõpetas ravikuuri ja kelle rögakülvid olid ravi lõppedes negatiivsed. MDR-TB ja XDR-TB juhtude seas olid "paranenud" need, kes lõpetasid ravikuuri vastavalt ravijuhendile ja olid vähemalt viimase 12 ravikuu vältel püsivalt bakterioloogiliselt negatiivsed. Ravikuuri lõpetasid haiged, kes läbisid ravikuuri vastavalt ravijuhendile, kuid ei vastanud paranemise definitsioonile bakterioloogiliste uuringute puudumise tõttu. Ravitulemused "paranenud" ja "lõpetas ravikuuri" summeerusid "positiivseks ravitulemuseks" (II).

TB-patsientidel, kes surid TB-ravi ajal ükskõik millisel põhjusel, oli ravitulemuseks "suri". Patsiendid, kes katkestasid ravikuuri enamaks kui 2 kuuks, klassifitseeriti "ravi katkestajateks". "Mitteefektiivse ravi" lõppega olid patsiendid, kui vähemalt 2 viimasest 5-st rögakülvist viimase 12 ravikuu jooksul olid positiivsed või vähemalt 1 viimasest 3-st röga-külvist oli positiivne. Ravitulemused "suri", "ravi katkestaja" ja "mitteefektiivne ravi" kombineeriti "negatiivseks ravitulemuseks" (II). Patsiendid, kes kolisid ravikuuri ajal Eestist ära klassifitseeriti "lahkus Eestist" ning jäeti vastavalt protokollile uuringust välja.

Ravi efektiivsust hinnati positiivse ravitulemusega patsientide osakaaluga ja DOTS-Plus programmi kliinilist tõhusust positiivse ravitulemusega patsientide osakaaluga jättes arvestamata ravikatkestajate ravitulemuse (II).

Andmete kogumine ja statistiline andmetöötlus

Uuringu andmebaasi koostamise aluseks oli TB-registri andmebaas, mis põhines TB-patsientide raviarstide poolt ja laboratooriumitest TB-registrisse saadetud andmetel. Puuduvad andmed koguti hiljem täiendavalt labori andmebaasist ning patsientide ravidokumentatsioonist. TB-haigete kohta koguti demograafilisi andmeid (vanus, sugu, haridustase, sünnikoht, elamine maal või linnas), sotsiaal-ökonoomilisi andmeid (perekonnaseis, elukoht, varasem kinnipidamiskohas viibimine, andmed tööhõive kohta, ravikindlustuse olemasolu ja andmed alkoholi kuritarvitamise kohta), TB-ga seotud andmed (varasem TB-ravi, teadaolev kontakt TB-ga, röga bakterioskoopilise uuringu tulemus, lagunemiste olemasolu ravi alustamise eelselt tehtud rindkere röntgenogrammil, haigustekitaja kuulumine W-Beijing'i genotüüpi, resistentsus testitud TB-ravimite suhtes ja haiguse avastamise meetod) ning HIV-testi tulemusi.

Ravi katkestamise põhjuste väljaselgitamiseks küsitleti patsiente ravinud arste ja patsientide surma ajad ning põhjused kontrolliti surma põhjuste registri andmebaasist. Lähteandmete omavahelisel võrdlemisel kasutati Pearson'i χ^2

testi (kategooriamuutujate analüüsiks) ja Mann-Whitney U-testi (pidevmuutujate analüüsiks). Riskitegurite analüüs teostati mitmemõõtmelise logistilise regressioonanalüüsi meetodil, surma riskitegureid analüüsiti ravi katkestajatel Cox'i regressioonanalüüsi meetodil. Statistiliseks andmetöötluseks kasutati SPSS tarkvara versiooni 10.1 (Chicago, IL, USA).

TULEMUSED

Uuringusse kaasati 1163 patsienti, kellest 935 (80,4%) olid uued haigusjuhud ja 228 (19,6%) retsidiivjuhud. Kõikidest uuritavatest 907 (78,0%) olid mitte-MDR-TB juhud, 196-l patsiendil (76,6%) oli MDR-TB ja 60-l haigel (5,2%) oli XDR-TB. Kõikidest uuritutest olid haigustekitajad tundlikud kõikidele esimese rea TB-ravimitele 722 (62,1%) patsiendil, kuid MDR-TB haigetel olid haigustekitajad resistentsed keskmiselt 5,7-le (vahemik 2–10) ja XDR-TB haigetel 6,9-le (vahemik 5–10) TB-vastasele ravimile.

Patsientide vanuse mediaan oli 45,3 aastat ning kõikidest haigetest 72,5% (843) olid mehed. Eestis oli sündinud 917 patsienti (78,9%), 92 (7,9%) haigetest olid kodutud, 463 patsienti (39,8%) olid töötud ja 228 (19,6%) olid viibinud kinnipidamisasutuses. Alkoholi kuritarvitamine oli registreeritud 462-l juhul (39,7%). Kõikidest haigetest 877-l (75,4%) oli TB avastatud sümptomite tõttu arsti poole pöördumisel, 674 (58,0%) olid bakterioskoopiliselt positiivsed ravi alustamisel ning 810-l (69,7%) oli lagunemine ravieelselt tehtud kopsude röntgenogrammil. Kõikidest haigetest 54 (4,7%) olid HIV-infitseeritud.

MDR-TB ja XDR-TB riskifaktorid (I)

XDR-TB riskiteguriteks olid varasem TB-ravi, HIV-infektsioon, kodutus ja alkoholi kuritarvitamine. MDR-TB riskiteguriteks osutusid varasem TB-ravi ja vanus alla 65 eluaasta.

Patsientide vanusegrupis ≤ 24 aastat moodustasid kõikidest haigetest 57,1% naised (üldpopulatsioonis oli naiste osakaal 38,0%). Nimetatud noorimas vanusegrupis osutusid MDR-TB riskifaktoriteks naissugu ja sündimine väljaspool Eestit.

TB-haigete ravitulemused

235-st MDR-TB haigest paranes või lõpetas ravikuuri 60,4% ja hea ravisoostumusega patsientide hulgas oli ravi efektiivsus 72,8%. Uute haigusjuhtude ravi tulemus oli võrreldes korduvravijuhtudega statistiliselt oluliselt kõrgem (71,0% 47,1% vastu) ning mitteefektiivse ravi osakaal (vastavalt 4,6% ja 15,4%) ja suremus (vastavalt 7,6% ja 20,2%) olid madalamad.

XDR-TB haigete hulgas lõpetas ravi edukalt 42,6% haigetest ning ravi efektiivsus oli 50,0%. Võrreldes MDR-TB haigetega oli XDR-TB haigete paranemise osakaal oluliselt madalam ($p = 0,002$) ning madalam oli ka ravi efektiivsus ($p < 0,001$).

MDR-TB ja XDR-TB patsientide negatiivse ravitulemuse riskifaktorid

MDR-TB haigete negatiivse ravitulemuse riskifaktoriteks osutusid HIV-infektsioon, varasem TB-ravi, resistentsus ofloksatsiini suhtes ja bakterioskoopiliselt positiivne röga äigepreparaat ravi alguses. XDR-TB patsientide negatiivse ravitulemuse riskiteguriteks olid elamine linnas ning bakterioskoopiliselt positiivne röga äigepreparaat ravi alguses.

TB ravikatkestamise osakaal ja põhjused

Kõikidest ravi alustanud patsientidest katkestas ravi 9,4%. Uute TB-juhtude hulgas oli katkestajate hulk võrreldes eelnevalt ravi saanud TB-haigetega statistiliselt madalam ($p < 0,001$), samuti oli katkestajate osakaal suurem MDR-TB haigete hulgas võrreldes mitte-MDR haigetega ($p < 0,001$).

Kõige levinum TB-ravi katkestamise põhjus oli alkoholi kuritarvitamine (77,9%). Ravi kestvuse mediaan ravi algusest ravi katkestamiseni oli 142,5 päeva (vahemik 2–994), vastavalt 124,5 päeva mitte-MDR-TB haigetel (vahemik 11–450 päeva) ja 241,5 päeva MDR-TB haigetel (vahemik 2–994 päeva).

TB ravi katkestamise riskitegurid

TB-ravi katkestamise riskiteguriteks osutusid alkoholi kuritarvitamine, töötus, MDR-TB, linnas elamine ja varasem kinnipidamisasutuses viibimine.

Mitte-MDR-TB haigete hulgas olid ravi katkestamise riskiteguriteks töötus, alkoholi kuritarvitamine, varasem TB põdemine ja linnas elamine, kuid ravi alguses positiivse röga äigepreparaadiga juhtude hulgas osutus ravi katkestamise risk väiksemaks. MDR-TB haigete hulgas oli ainsaks ravi katkestamise riskiteguriks töötus.

Elulemus pärast TB ravi katkestamist ja suremuse riskitegurid

104-st ravi katkestajast 102 kohta õnnestus koguda infot ravi katkestamise järgse seisundi kohta. Neist 4 (3,9%) olid paranenud, 6 (5,9%) jätkasid TB ravi

andmete kogumise lõpetamisel (31. oktoober 2008) ja 30 (29,4%) surid ravi katkestamise järel. Surnutest 16 patsienti (53,3%) surid TB tõttu, kusjuures 68,8% neist olid MDR-TB haiged. Patsientide elulemuse mediaan pärast TB-ravi katkestamist oli 342,0 päeva (vahemik 28–1021 päeva).

Töötus oli nii TB-ga seotud kui ka muudel põhjusel saabunud surma riskiteguriks. TB-st tingitud surma riskiteguriteks osutusid HIV-infektsioon, MDR-TB, varasem TB põdemine ja bakterioskoopiliselt positiivne röga äigepreparaat ravi alustamisel.

JÄRELDUSED

1. XDR-TB riskiteguriteks olid varasem TB ravi, HIV-infektsioon, kodutus ja alkoholi kuritarvitamine. MDR-TB riskiteguriteks olid varasem TB ravi ja vanus alla 65 aasta. Alla 24-aastaste patsientide hulgas oli MDR-TB seotud naissoo ja sünnikohaga väljaspool Eestit.
2. MDR-TB haigetest paranes või lõpetas ravikuuri 60,4% ja XDR-TB haigetest vastavalt 42,6%. MDR-TB haigete negatiivse ravitulemuse riskifaktoriteks olid HIV-infektsioon, varasem TB ravi, resistentsus ofloksatsiinile ja bakterioskoopiliselt positiivne röga äigepreparaat ravi alguses. XDR-TB haigete negatiivse ravitulemuse riskiteguriteks olid linnas elamine ja bakterioskoopiliselt positiivne röga äigepreparaat ravi alguses.
3. Ravikuuri katkestas 9,4% kõikidest haigetest ning katkestajate osakaal MDR-TB haigete hulgas oli 17,0%. Kõige sagedasem ravi katkestamise põhjus oli alkoholi kuritarvitamine (77,9%) ning ravi katkestamise riskifaktoriteks olid alkoholi kuritarvitamine, töötus, linnas elamine ja varasem kinnipidamisasutuses viibimine.
4. Kõikidest ravi katkestajatest 29,4% surid ravi katkestamise järgselt ning töötus oli seotud nii TB-st tingitud suremusega kui ka surmadega muudel põhjustel. HIV-infitseeritus, MDR-TB, varasem TB põdemine ja bakterioskoopiliselt positiivne röga äigepreparaat ravi alguses olid TB-ga seotud suremuse riskiteguriteks.

Tulemustest järeldub, et nii ravi katkestamise põhjused kui surma riskitegurid ravi katkestamise järel on inimeste poolt mõjutatavad asjaolud. Parandamaks Eestis ravimresistentse TB-ga haigete ravitulemusi ning vähendamaks seeläbi ravimresistentse infektsiooni levikut ühiskonnas on oluline pöörata erilist tähelepanu varasemalt TB ravi saanud patsientidele, HIV-infitseeritutele ning sotsiaalselt haavatavatele patsientidele (töötutele, kodututele, alkoholi kuritarvitajatele jne) parandamaks nende ravisoostumist.

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Since 2003	Tartu University Lung Clinic, pulmonary physician
Since 2003	National Institute for Health Development, National Tuberculosis Programme manager

Scientific experience

The main research interest is epidemiology of drug-resistant tuberculosis. 7 scientific publications in international peer reviewed journals and 7 presentations at international congresses.

Membership:
- The Estonian Respiratory Society (member of the Board)
- The European Respiratory Society
- The International Union Against Tuberculosis and Lung Disease

CURRICULUM VITAE

Kai Kliiman

Kodakondsus: Eesti
Sünniaeg ja -koht: 28. detsember, 1969 Tartu, Eesti
Perekonnaseis: abielus, 3 last, sündinud 1990, 1995 ja 1997
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Haridus

1976–1987	Tartu 5. Keskkool
1987–1994	Tartu Ülikooli Arstiteaduskond, ravi eriala, *cum laude*
1994–1999	Internatuur Tartu Ülikooli Kliinikumis
1999–2003	Residentuur Tartu Ülikooli Kliiniku Kopsukliinikus
2004–2010	Tartu Ülikooli Kopsukliinik, doktorantuur

Erialane teenistuskäik

Alates 2003	SA Tartu Ülikooli Kliinikum, Kopsukliinik, pulmonoloog
Alates 2003	Tervise Arengu Istituut, riikliku tuberkuloositõrje programmi juht

Teadustegevus

Peamine uurimisvaldkond on ravimresistentse tuberkuloosi epidemioloogia. Ilmunud 7 teaduspublikatsiooni ja 7 ettekannet rahvusvahelistel kongressidel.

Kuulumine erialastesse organisatsioonidesse:
- Eesti Kopsuarstide Selts (juhatuse liige)
- Euroopa Kopsuarstide Assotsiatsioon (ERS)
- Rahvusvaheline Tuberkuloosi ja Kopsuhaiguste Vastane Liit (IUATLD)

DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS

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