DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS
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EPIDEMIOLOGY OF TUBERCULOSIS IN ESTONIA 1991–2003 WITH SPECIAL REGARD TO EXTRAPULMONARY TUBERCULOSIS AND DELAY IN DIAGNOSIS OF PULMONARY TUBERCULOSIS

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LIST OF ORIGINAL PUBLICATIONS

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

I Pehme L, Hollo V, Rahu M, Altraja A. Tuberculosis during fundamental societal changes in Estonia with special reference to extrapulmonary manifestations. Chest 2005;127:1289–1295.

II Pehme L, Altraja A, Hollo V, Rahu M. Kopsuväline tuberkuloos Eestis. Eesti Arst 2003;82:686–692.

III Pehme L, Rahu K, Rahu M, Altraja A. Factors related to patient delay in pulmonary tuberculosis in Estonia. Scand J Infect Dis 2006;38:1017–1022.

IV Pehme L, Rahu K, Rahu M, Altraja A. Factors related to health system delay in pulmonary tuberculosis in Southern Estonia. Int J Tub Lung Dis 2007;11:275–281.

ABBREVIATIONS

AFB	Acid-fast bacilli
ATS	American Thoracic Society
AIDS	Acquired immune deficiency syndrome
BCG	Bacille Calmette-Guérin
CI	Confidence interval
DOTS	Directly observed treatment strategy
EPTB	Extrapulmonary tuberculosis
GPSTB	Global Plan to Stop TB
HIV	Human immunodeficiency virus
HSD	Health system delay
ISTC	International Standards for Tuberculosis
MBT	*Mycobacterium tuberculosis*
MDR-TB	Multidrug resistant tuberculosis
NTP	National Tuberculosis Program
OR	Odds ratio
RR	Relative risk
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively resistant tuberculosis

DEFINITIONS

Adolescents – individuals between 15 and 17 years of age.

Adults – individuals ≥18 years of age.

Case of tuberculosis – a patient in whom tuberculosis (TB) has been confirmed by bacteriology or diagnosed by a clinician.

Children – individuals between 0 and 14 years of age.

Delay in diagnosis – the interval in days from the date of onset of whatever first reported symptom to the date the TB diagnosis was made. It consists of patient delay and health system delay.

Extensively resistant tuberculosis (XDR-TB) – the strain of *Mycobacterium tuberculosis* is resistant to isoniazid and rifampicin (MDR), as well as to any fluoroquinolone and at least 1 of 3 injectable second-line drugs (amikacin, kanamycin or capreomycin) [1].

Extrapulmonary tuberculosis (EPTB) – TB of organs other than lungs (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges etc.); when both pulmonary TB and EPTB are diagnosed, the case should be classified as a pulmonary case [2, 3].

Extreme health system delay – a health system delay greater than the 75th percentile of the length of the health system delay.

Extreme patient delay – a patient delay greater than the 75th percentile of the length of the patient delay [4].

Health system delay (HSD) – the interval in days from the date when a medical provider was first contacted by the patient to the date the TB diagnosis was made [5–7].

Multidrug resistant tuberculosis (MDR-TB) – the strain of *Mycobacterium tuberculosis* is resistant to at least isoniazid and rifampicin [8].

New case of tuberculosis – a patient who has never received treatment for TB or who has taken anti-TB drugs for less than 1 month [2, 9]. Cases reported as "history unknown" in the European Region are included as new cases [2, 10].

Passive case finding – case detection among symptomatic patients self-reporting to health service.

Patient delay – the interval in days from the date of onset of whatever first reported symptom to the date of the patient's first visit to a health care provider [5, 6].

Prolonged health system delay – a health system delay greater than the median of the length of the health system delay.

Prolonged patient delay – a patient delay greater than the median of the length of the patient delay [11].

Pulmonary tuberculosis – all forms of TB, when disease involves the lung parenchyma; when both pulmonary TB and EPTB are diagnosed, the case should be classified as a pulmonary case [2].

Resistance among cases never treated – primary drug resistance due to infection with resistant bacilli [8].

Resistance among previously treated cases – acquired drug resistance

Total delay – the interval in days from the date of onset of whatever first reported symptom to the date the TB diagnosis was made [6].

WHO regions – for the analysis, countries are grouped into six WHO regions: African Region, the Region of the Americas, the Eastern Mediterranean Region, the European Region, the South-East Asia Region and the Western Pacific Region. However, to make clear the differences in epidemiological trends within regions, Africa is subdivided into two regions comprising countries with high HIV infection rates (≥4% in adults aged 15–49 years) and those with low rates of HIV infection (<4%); WHO also distinguishes central from eastern Europe (countries of the former Soviet Union plus Bulgaria and Romania) and combine western European countries with the other established market economies [2, 12, 13].

1. INTRODUCTION

Tuberculosis (TB) will remain a major concern for public health worldwide [12]. In Western Europe, TB incidence rates slowed their previous decline [14]. Estonia, like other Baltic and Eastern European countries, experienced a resurgence of TB after its independence was declared in 1991. The worsening of the TB incidence is due to economic decline, increased poverty, social disruption and sub-standard health services [15, 16]. In Estonia, following a long-lasting steady decline in incidence from 417 per 100 000 of population in 1954 to 26 in 1992, the incidence rate showed a steady increase reaching 59/100 000 in 1998. Fortunately, after that, the incidence rate declined and reached 52/100 000 in 2001 and 36 in 2005 [2, 3]. The incidence of TB among children rose simultaneously from 1.2/100 000 in 1993 to 5.2/100 000 in 2000 and decreased to 1.1 in 2004. Quite soon it became evident that multidrug resistant TB (MDR-TB) represents a serious problem in Estonia: the proportion of MDR-TB among new cases increased from 10.2% in 1994 to 14.1% in 1998 [17] and to 13.3% in 2005 [18, 19]. The proportion of acquired MDR-TB (among previously treated cases) was 19.2% in 1994, 14.5% in 1998 and 41.5% in 2004 [17, 18, 20].

Importantly, the most often reported reasons for the resurgence of TB, such as immigration and human immunodeficiency virus (HIV) positivity, did not play a major role in the increasing incidence of TB in Estonia. The first case of HIV infection in Estonia was registered in 1988, with the breakthrough occurring in 2000, when 390 persons in Estonia were diagnosed as HIV-positive [21, 22]. The first cases of co-infection of TB and HIV was diagnosed in 1997 and since 1999, the majority of the TB patients have been tested for HIV-positivity (91% in 2005). As a result, 99 cases of co-infection of TB and were reported by 2005 [18, 19]. As a former part of the Soviet Union, Estonia was untouched by global immigration, but received immigrants from other Soviet republics, mostly from Russia.

Although strengthening TB surveillance has become a public health priority in Europe [14], there are still few reports on the epidemiology of extra-pulmonary TB (EPTB) during the last decade in non-HIV-infected populations [23, 24] with a concomitant increase in pulmonary TB.

Timely diagnosis of active TB is particularly crucial to minimize disease transmission, but also morbidity and mortality in the community, as well as within health care facilities [25, 26]. Although novel and improved drugs, methods of diagnosis and vaccines are developed eventually that could markedly decrease the global burden of TB. Until now, the cornerstone of the control of TB is based on interruption of its transmission through rapid identification and cure of infectious cases [13]. Styblo estimated that untreated sputum smear-positive cases infect about 10 other individuals each year [27, 28]. In line with this noting, delayed or missed diagnosis has been reported to

be an important factor in the occurrence of nosocomial outbreaks of TB [29–31]. The delay in diagnosis has two constituent components: patient delay, defined as a time interval between onset of the patient's first reported symptom and reporting to the health facility or referral to the physician, and health system delay (HSD) or doctor delay, which is an interval from the first medical visit to the date the disease was diagnosed [5, 32]. Thus, better knowledge of the factors that influence these delays is crucial for controlling TB. It seems logical to assume that high prevalence of pulmonary TB in a society makes reference to a prolonged delay with the diagnosis of TB as a reason. On the other hand, delay in the diagnosis of pulmonary TB appears not to be specifically related to the prevalence of TB itself, since considerable delays have been described in both high- and low-prevalence countries [33]. Instead, wider societal and health system issues in Eastern Europe are critically required and TB control should be shaped to individual country needs [1].

It is recognized that much of the spread of TB may take place before the first contact with the medical care [34]. Former studies indicate that a great variety of risk factors are associated with prolonged patient delay, especially with "barriers" in accessing health care such as living in rural areas [7, 35, 36], unemployment and missing health insurance [34, 37, 38], immigration and language barriers [39]. Advanced age and various related factors [4, 7, 11, 40], lower level of education [26, 35], female gender [4] and inadequate wisdom about TB [6, 41] have been associated with prolonged patient delay as well.

Numerous risk factors for prolonged HSD in TB have been identified in previous studies, they include individual's perception of the disease, severity of the disease, access to health services and expertise of the health personnel [7]. There is, however, limited data about the readiness of health care system to manage TB after overwhelming political changes, which followed the reformation of the health system. Substantially new principles of the health care system were implemented after 1991, resulting from social, economic and political reformations. The main changes included replacement of the state-funded health care system by a health insurance that does not automatically cover the whole population leaving the unemployed people uninsured. In Estonia, a system of family doctors was created and opportunities for private doctors were opened during the health care reformation. One of the six key elements of the StopTB strategy is involving all relevant health care providers – public and private – in providing effective TB services [1]. From 1998, almost 400 primary care doctors started to work as independent or joined practitioners [42] although the competence of family physicians in the process of TB evaluation is still unclear in a society that has undergone such health system reformation.

Principal reformations took place in TB management with creation of the Estonian National TB Program (NTP) in 1997. NTP co-ordinates all TB activities in the country and is responsible for Estonian Tuberculosis Registry,

laboratory services, Directly Observed Treatment, anti-TB drug supply and training [43]. The impact of outpatient treatment of TB increased and the number of hospital beds for TB patients decreased from 875 in 1991 to 291 in 2000, and all 250 TB sanatoria beds were removed. Instead of former specialised TB dispensaries, patients with symptoms of TB should now turn to the family doctor or directly to the chest physician.

Despite these changes, the practice and principles of diagnosing pulmonary TB and EPTB did not undergo any significant alteration during the period of the current study (1991–2000). The management of TB in Estonia based on the directly observed treatment strategy (DOTS), greatly contributed to improved global TB control during the past decade [16, 44–46]. Despite, the DOTS strategy has been fully implemented in Estonia since 2000 and works on the optimal level, there could be other patient and health-system factors, retarding the detection of the TB cases and the quickness of TB diagnosis, these factors vary nationally and internationally [1, 47, 48]. This study was designed (1) to analyse the incidence and distribution of cases of TB by age, gender, site and bacteriological confirmation in Estonia between 1991 and 2000, a period that reflected a low prevalence of immigration and HIV infection and increasing incidence of pulmonary TB, and (2) to assess the patient delay and HSD in pulmonary TB and its risk factors characteristic of a country, which has undergone overwhelming political changes and complete modification of health care system accompanied by increasing incidence of pulmonary TB.

2. REVIEW OF THE LITERATURE

2.1. Epidemiology of Tuberculosis

2.1.1. Global Epidemiology

According to WHO, one third of the population of the world is infected with TB bacilli and 5–10% of those develop symptomatic TB during their lifetime. According to WHO calculations, in 2004, the total number of prevalent cases of TB worldwide was 14.6 million (229/100 000). The total number of new cases of TB has increased from 7.96 million in 1997 to 8.9 million in 2004, including 3.5 and 3.9 million sputum smear-positive cases, the most infectious form of the disease, respectively [2]. About 80% of individuals with newly diagnosed disease live in the 22 most populous countries [49] and the largest number of cases (2.95 million) accounted for the South-East Asian region followed by the Western Pacific region (1.96 million). Bangladesh, China, India, Indonesia and Pakistan together account for one half (48%) of the new cases that arise every year. The European and American regions had the fewest cases, both in total numbers and per capita [47, 49]. Nine of the 22 highest-burden countries are located in two areas of the world, where TB incidence is rising rapidly. Eight are in sub-Saharan Africa and the ninth, Russia, is at the heart of the former Soviet Union [13]. The global TB incidence was 79/100 000 in 2005 [3].

Despite the TB incidence rate was stable or falling in five out of the six WHO regions, being 27/100 000 in Region of Americas, 40/100 000 in European Region, 46/100 000 in the Eastern Mediterranean Region, 67/100 000 in the Western Pacific Region and 103/100 000 in the South-East Asia Region [2, 49]. The WHO African region has the highest estimated incidence rate (356/100 000 and 163/100 000 in countries with high and low rates of HIV infection, respectively).

The global TB incidence was growing at 0.6% between 2003 and 2004, the last year for which data are available [16]. This is a slower rate of growth than in previous years (worldwide, the incidence rate of TB was growing at a maximum of 1.2% per year), but is still alarming [1]. This continued increase is largely the result of the striking increase in cases in sub-Saharan Africa and, to a lesser extent, in the former USSR [16]. Whilst the worsening of the TB incidence in Africa is due to the HIV epidemic compounded by an insufficient health infrastructure, it is due to different causes in Eastern Europe, including economic decline, social disruption and sub-standard health services [15, 16].

It has been assumed that the trends in incidence to 2003 will continue until 2015, generating more than 10 million new cases in that year [12]. The global incidence rate will reach about 150/100 000 in 2015. If Africa and Eastern

Europe are excluded from the global statistics, the prevalence rate in 2015 would be equal to about half of that what it was in 1990.

Because few countries with high burden of TB compile reliable statistics on the cause of death, the global and regional trends in TB deaths are uncertain. However, the findings of one assessment based on modelling indicate that death rates from TB could have been falling since around year 2000, after rising during the 1990s [2, 12]. As estimated, 1.7 million people died from TB in 2004 (1.87 million in 1997), including 264 000 patients who were co-infected with HIV [2, 12, 50, 51]. Between 2002 and 2003, the TB death rate fell by 2.5% overall and by 3.5% among HIV-negative patients. In the European region, 445 000 new TB cases and nearly 70 000 deaths were estimated to have resulted from TB in 2004 [16].

Europe remains divided between West and East also in terms of TB incidence. Incidence rates in Western Europe were below 25/100 000 in 1997 and in 2004 as well. In Eastern Europe, the rates were more than 30/100 000, except in Czech Republic (20/100 000) and more than 70/100 000 in Romania, the Russian Federation, Moldova and the five republics of central Asia [2, 47]. In Eastern Europe, the incidence rate increased during the 1990s, peaked around 2001 and has since fallen slightly [1]. The downturn in case notifications in Eastern Europe is clear based on data from Russia, Belarus and the Baltic countries, although incidence rates might still be increasing in the central Asian republics of Kyrgyzstan, Kazakhstan, Tajikistan and Uzbekistan [16, 49]. WHO projections assume that from 2003 onward, the incidence rate will continue to decrease by 4% annually, which is approximately the same rate as observed from 1980–1990 before the collapse of the Soviet Union.

In 1997, WHO and International Union Tuberculosis and Lung Disease reported for the first time standardized information on drug resistance from surveys or surveillance systems conducted since 1994 in 35 countries [17, 52]. This information confirmed that drug resistance was widespread and MDR-TB was a critically high level in some parts of the world, especially in some countries of the Soviet Union.

About 3% of all the new TB cases that arise worldwide every year are estimated to be multidrug resistant [53]. The frequency among previously treated cases is higher [49]. The prevalences of MDR-TB in Western Europe are very low, while in the former Soviet republics of Latvia, Estonia and Russia, some of the highest prevalences in the world have been detected [14, 54–56]. Based on the results of periodic surveys, more than 10% of new TB cases in Estonia, Latvia and some parts of Russia are multidrug resistant [17, 57]. Drug resistance is most probably a product of the same events, which led to TB resurgence in these countries, not the primary cause of it [49].

Co-infection of Mycobacterium tuberculosis and HIV

HIV is a major hindrance to TB control [58, 59]. HIV may alter the epidemiology of TB in three different ways: 1) endogenous reactivation of pre-existing infection with *Mycobacterium tuberculosis* in persons, who become infected with HIV; 2) progression from infection with *Mycobacterium tuberculosis* to TB in persons with pre-existing HIV infection; 3) transmission of tubercle bacilli to the general population from TB patients who developed TB because of HIV infection [60, 61]. The proportion of TB cases with HIV infection has certainly been rising during the 1990s. Co-infection of *Mycobacterium tuberculosis* and HIV has been diagnosed in 8% and in 11% of incident TB cases among adults worldwide in 1997 and 2005, respectively; the respective total figures are 640 000 cases in 1997 and 628 615 in 2005 [2, 3, 47]. The burden of HIV is outstandingly high in sub-Saharan Africa (32% of TB cases infected), though there is great variation among African countries (0–75%). The proportion of TB cases with simultaneous HIV co-infection in Western European Region varies from 1.8% in Denmark and 4.5% in Belgium to 8.3% in Iceland and 15.7% in Portugal. Unfortunately, the proportion of unknown HIV status among TB patients in these countries varies from 33% in Iceland to 96% and 98% in Belgium and Denmark, respectively. HIV has spread rapidly in the Eastern Europe Region since the late 1990s. An estimated proportion of 50–90% of HIV infections in Eastern Europe and Central Asia is caused by intravenous drug abuse [1]. HIV-positive TB patients out of all TB cases in Estonia, Latvia and Lithuania in 2004 formed 4.4%, 2.5% and 0.3%, respectively. TB cases with unknown HIV status in these countries formed 20%, 97% and 0%, respectively [18].

Tuberculosis and Migration

Increased international migration will further contribute to TB morbidity in many industrialised countries and the proportion of foreign-born patients steadily increases in these countries [62]. An experience from Sweden has demonstrated that the number of reported cases among the Swedish-born population continuously decreased from 1984 to 1993, the number of TB cases among the foreign-born one increased rapidly during the same observation period. As a result, the total number of cases has remained stable [60]. In Sweden, the proportion of foreign-born individuals among the TB cases increased from 60% in 1998 to 74% in 2004 [8, 18, 20].

2.1.2. Tuberculosis Epidemiology in Estonia

During the years following the Second World War, the incidence rate of TB peaked in 1953 with 417/100 000 [43]. Due to improved TB control work and the improvement in the living conditions of population, the long-lasting steady decline in incidence of TB followed since 1954. Estonia experienced a resurgence of TB after independence was declared in 1991. In particular, the TB incidence rate increased from 26.0/100 000 in 1992 to 59/100 000 in 1998. After that, it declined and reached 52/100 000 in 2001 and 36/100 000 in 2005 [3].

The total number of TB cases, notified in 1991 was 406, increased to 820 in 1998 and reached to 479 in 2005 [3]. The data about TB cases in penitentiaries has been available for countrywide Estonian Tuberculosis Registry since 1996 and their proportion was 7.3% out of all cases of TB in Estonia in 2004. The total number of TB cases among children 0–14 years rose simultaneously from 4 cases in 1992 to 10 cases in 1998 and declined again to 2 in 2004 and 1 in 2005 [19, 63]. The main reasons for failure of TB control after 1991 in Estonia could be inadequate political commitment; under-funding of TB services and slow progress for implementing internationally recommended control strategies. In reality, wide-ranging changes in health policy destabilized or disrupted efforts to control TB [17, 64]. The most often reported reasons for the resurgence of TB, such as immigration and HIV-positivity, were absent did not therefore play a major role in the increased incidence of TB in Estonia. The proportion of pulmonary TB has been 83–91% during last 15 years.

The incidence of smear positive TB cases in 2005 was highest in the age groups 45–54 and 25–34 years, being 27/100 000 and 19/100 000, respectively [2, 3]. Male individuals among all TB cases formed 71% in 2004 (male-female ratio 2.4) [18]. Roughly one half of the cases of pulmonary TB (48%) were smear positive. The proportion of culture-confirmed diagnosis varied by the site of disease and was 80% in pulmonary and 42% in extrapulmonary cases [18]. The susceptibility data of all *Mycobacterium tuberculosis* isolates from pulmonary TB cases have been available since 1994. MDR-TB is a serious health care issue in Estonia: out of all isolates tested for drug sensitivity, primary multidrug resistance increased from 10.2% in 1994 to 14.1% in 1998 and to 13.3% in 2005. The proportion of acquired MDR-TB (among previously treated cases) was 19.2% in 1994, 14.5% in 1998 and 52.1% in 2005 [17–20]. An increased risk of nosocomially transmitted TB among health care workers in Estonia has been reported in previous studies. Krüüner and co-authors [65] have found that the incidence of TB among health care workers during the 5-year period 1994–1998 was 1.5 to three times higher than in the general population (incidence rate 91/100 000). A total of 67 new cases of active TB were registered among health care workers during the study period. Among the 47 *Mycobacterium tuberculosis* isolates available for susceptibility testing, 23

(49%) were resistant to at least one of the first-line drugs, 18 (38.3%) isolates were MDR-TB

Co-infection of Mycobacterium tuberculosis and HIV in Estonia

The prevalence of HIV infection in Estonia was negligible until late 1990s with the breakthrough occurring just in 2000, when 390 HIV-positive persons in the whole population in Estonia were diagnosed. The number of newly registered HIV infections peaked in 2001 (1474 incident cases), after that the total number of HIV-infected people decreased and reached 668 in 2006 [66].

The first cases of TB and HIV co-infection in Estonia were diagnosed in 1997, and since 1999, the vast majority of TB patients have been tested for HIV-positivity (91% in 2005) [19]. As a result, 99 cases of TB and HIV co-infection have been reported by 2005. The proportion of HIV positive patients out of all TB cases in Estonia increased from 0.1% in 2000 to 2.8%, 2.9% and 6.4% in 2002, 2003, 2005, respectively [18, 19, 67].

Tuberculosis and Migration in Estonia

Since Estonian frontiers were closed for global immigration until 1991, the impact of immigration in Estonia has been insignificant and foreign immigrants, particularly those from high-incidence countries, still have not influenced TB epidemiology in Estonia. Formerly, Estonia got immigrants mostly from other parts of the Soviet Union. Up to present, 99% of immigrants are of Eastern European origin, only 1% has come from Western Europe. Although 15.8% of all TB patients in Estonia were foreign-born in 2005 [2], only one patient had lived in Estonia for less than 5 years.

2.2. Transmission of Tuberculosis

2.2.1. Transmission of Infection from Person to Person

TB spreads from person to person through the air by droplet nuclei. A patient with pulmonary or laryngeal TB produces droplets when talking, coughing, sneezing or singing [60]. Droplet nuclei represent air-dried particles of 1–5 μm in diameter that contain *Mycobacterium tuberculosis* complex [68]. Coughing is the most important way in spreading TB infection: one cough is the equivalent of about 5 minutes of loud talking in terms of the resulting number of droplet nuclei, about half of which are still suspended in air 30 minutes after coughing [69, 70].

Patients with sputum smears positive for acid-fast bacilli on direct microscopy are the major sources of infection in community [60, 71, 72], because it requires 5000–10000 bacilli in 1 millilitre of specimen to allow the detection of bacteria in stained smears [73–75]. In contrast, 10 to 100 organisms are needed for a positive culture [76]. A study in San Francisco demonstrated that 17% of transmissions were attributable to index cases with sputum smears negative at diagnosis and the relative transmission rate for smear-negative compared to smear-positive TB was 0.22, i.e., roughly one fifth of transmissions [77]. After inhalation, the droplet nucleus is carried down the bronchial tree and implants in a respiratory bronchiole or alveolus

[78]. Whether or not an inhaled tubercle bacillus establishes an infection in the lung depends on both the bacterial virulence and the inherent microbicidal ability of the alveolar macrophage that ingests it [68, 79].

2.2.2. Risk of Infection

The rate of transmission of tubercle bacilli is dependent on the number of sources of infection in a society. The risk to a susceptible individual of becoming infected depends on the density of tubercle bacilli in inhaled air and the duration of exposure to the air. However, the relation between infectious cases and risk of infection is determined primarily by the duration of infectiousness rather than the incidence of cases [80, 81]. In the absence of control measures (case finding and anti-TB chemotherapy), each infectious case causes on average about 20 new infections, before death intervened or spontaneous bacteriologic conversion had occurred. Out of 20 new infections, two new TB cases will arise, one infectious and one non-infectious [13, 28, 82]. Risk of infection is intrinsically coupled to duration of undiagnosed, untreated and transmissible TB. As soon as an effective intervention is introduced, the duration of infectiousness is reduced, transmission is decreased and the relation between prevalence and incidence is disturbed. The relation between infectious cases and risk of infection is determined primarily by the duration of infectiousness rather than the incidence of cases [60]. This makes prolonged delays in the diagnosis and intervention important concerns. The most effective intervention for reducing infectiousness and the number of bacilli released into the air is treatment of cases, which reduces the infectiousness of even sputum smear-positive cases within a few weeks [83–87].

2.3. Different Sites of Tuberculosis

The cases of TB have been classified by the site of disease into two major groups:

Pulmonary case – a patient with TB disease involving the lung parenchyma. All TB cases were registered according to one single site of affection. A patient in whom both pulmonary and EPTB has been diagnosed should be classified as a pulmonary case [2].

Extrapulmonary case – a patient with TB of organs other than lungs (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges etc.).

Extrapulmonary Tuberculosis

TB has been classically regarded as a pulmonary disorder, but EPTB has become to constitute a progressively more significant share of the total morbidity from TB worldwide during the 20th century [88]. Worldwide, depending on age, gender, gender race and immunological competency, 10–70% of patients who develop active TB will manifest in organs other than lungs [89, 90]. A high incidence of EPTB has become somehow synonymous with the HIV infection, which is more prevalent in those with EPTB rather than with pulmonary TB [91–94]. EPTB comprises approximately 10–50% of all TB presentations in HIV-negative patients and 35–70% in HIV infected patients [95, 96].

Previous studies from other regions have shown that TB affecting extrapulmonary sites is more frequent in immigrants due to the high level of endemic TB in their countries of origin and to their poor living conditions [71, 89, 90, 94, 97–99]. EPTB is still more likely in Black and Asian patients [100, 101].

For TB in general, there are age-dependent differences by gender suggesting that endocrine changes may play a role in the risk of TB among infected persons [102]. Gender patterns of EPTB differ substantially from that in pulmonary disease. A male-female ratio in pulmonary TB is 2.1:1, whereas in EPTB, the ratio is only 1.1–1.3:1 [88, 103]. The highest proportion of EPTB among their total TB morbidity is noticed in the age group 0–14 years. Classical pulmonary TB is relatively uncommon in children in the USA [88]. Large differences have been found in susceptibility by age, race/ethnicity and gender for different sites of EPTB. Patients younger than 15 years of age are most likely to have lymphatic [104] and meningeal [105], but the likelihood of genitourinary TB and bone and joint TB increases along with increasing age. Pleural TB is diagnosed most likely in young adults.

Also, considerable differences were observed among race and ethnics groups with regard to the likelihood of EPTB at a particular site. The predominance of lymphadenitis in Asians [99] and genitourinary TB in Southern Europeans, particularly Italians [106], has been demonstrated in previous studies. The reasons for these distinctive patterns are not clear. In Black patients, the likelihood of developing genitourinary TB is only half of that among Non-Hispanic White patients, but with regard to developing miliary TB, the risk of Black patients is twice as high as in Caucasians [100].

Female patients are more likely to have lymphatic TB [24, 97, 100, 101, 107], but diverse results have been reported concerning other sites. Rieder with co-authors [100] have found that all forms of EPTB (except pleural TB) have been more likely to develop in female than male patients. The reasons behind this evidence are unknown.

The incidence of EPTB is considered to be quite constant in societies where immunocompromising infections are of low prevalence [24, 108, 109]. This results in a failure of EPTB to decline at the same rate as does pulmonary TB, as documented in studies that represent the pre-acquired immune deficiency syndrome (AIDS) era [24, 108, 109]. The relative frequency of EPTB is influenced by the changes in demographic characteristics of patients with TB in general, coupled with differences in the likelihood of developing EPTB among various groups of patients [100].

The proportion of cases reported without bacteriological confirmation differed by the site of the disease.

2.4. Symptoms of Pulmonary Tuberculosis

Despite, an active pulmonary TB may be present with no symptoms at all, in general, the great majority of the patients declare the presence of at least one symptom. Of the new cases of pulmonary TB, 90% of patients have been reported symptoms attributable to TB [39].

Systemic Symptoms

TB may produce symptoms and findings that are not specifically related to the organ or tissues involved, but are systemic in nature. Fever has been observed in patients with TB varies from approximately 37 to 80% [110–112]. Loss of appetite, weight loss, weakness and night sweats are also commonly admitted by patients with extensive disease and have been reported in more than half of patients with pulmonary TB [39, 113].

Pulmonary Symptoms

Symptoms of pulmonary TB include cough, sputum production, haemoptysis, chest pain and dyspnoea [78, 113]. Cough is the most common symptom of pulmonary TB. It is reported in 71–90% of cases [25, 39]. Anyone, who develops cough, or an exacerbation of cough that persists for more than 3 weeks, even if attributed entirely to cigarette smoking, should have a chest radiograph [113]. Early in the course of the illness it may be non-productive, subsequently, as inflammation and tissue necrosis ensue, sputum is usually produced. Sputum may be mucoid, purulent or blood-stained. Haemoptysis is a classic, but rarer symptom of pulmonary TB. Being present in 17–33% of cases [25, 39, 114], it may vary from mere blood-staining of sputum to rarer occurrence of sudden eruption of half litre or more of blood. Inflammation of the lung parenchyma adjacent to a pleural surface may cause pleuritic chest pain. Chest pain is common and may vary from a dull ache or tightness to severe pleuritic pain [113]. Dyspnoea could be unusual unless there is extensive disease [78], or could be found even in 40–56% of cases of pulmonary TB [25, 114]. With extensive pulmonary diseases, breathlessness may be a feature and endobronchial TB may result in localized wheeze or intrapulmonary stridor [115].

First Symptoms

Cough, fever and fatigue usually predominate more often amongst the first symptoms of patients with pulmonary TB, occurring in 62.9%, 23.7% and 8.2%, respectively [112].

2.5. Diagnosis of Pulmonary Tuberculosis

2.5.1. General Aspects

For proper establishment of the diagnosis of TB, chest X-ray, sputum microscopy, sputum culture and tuberculin skin test are required. The utilization of these methods depends on the traditions of TB management and economical situation in the country, as well as on the doctor's qualification. The question about the under-utilisation of smear microscopy, sputum culture or chest X-ray in the diagnosis of TB has been arisen in previous studies [25, 116]. Accordingly to performed studies, a significantly higher number of non-pulmonary specialists than pulmonary specialists used chest X-ray alone [116, 117]. The data from Korea and Japan demonstrated that 11–75% of diagnoses were done by hospitals and private health services only on the basis of X-ray

examinations [116] and this proportion was equal in both smear-negative and smear-positive cases [114].

Earlier studies have demonstrated a shorter HSD if the doctor had enquired about a history of TB in the family or household. Hence, usage of these low-cost investigations more widely should be recommended [25].

2.5.2. Diagnosis of Pulmonary Tuberculosis in Estonia

Every person in Estonia should have a personalized family doctor and persons with any kind of health problems in Estonia should firstly turn to his/her family doctor for medical help. If the suspicion of TB has arisen, persons can turn directly to chest physicians. In urgent health problems, patients use to call for ambulance, even if they have symptoms that include fever and cough. In emergencies and in case of TB or a suspicion of TB, all residents in Estonia have equally free access to public medical care including family doctors and pulmonary physicians, independently on their employment status, place of residence and nationality. The necessary medical expenditures are covered from the budget of the governmental Sick Fund. Private physicians could principally be involved in the process of the diagnosis of TB.

Sputum smear microscopy, sputum culture and chest X-ray are the obligatory tests for the diagnosis of pulmonary TB, but doctors usually start with X-ray as a rule. Doctors of all specialities are able to diagnose TB, but because of the practice that worked during many decades in Estonia, it could be best carried out at the departments or centres for TB. Chest physicians usually confirm the diagnosis of TB and keep contacts with the Estonian Tuberculosis Registry. Almost all Estonian doctors use to send patients with suspicion of TB to the chest physician as quickly as they can. The “loss of TB patients” could be further avoided by the system, according to which in addition to the doctors, also laboratories of mycobacteriology in Estonia have to send all information concerning smear and culture positive cases to the Estonian Tuberculosis Registry.

The majority of patients, 74.2% out of all TB cases in 2004, sought medical care because of their symptoms, 20.7% were detected during routine prophylactic examinations and 4.1% during contact investigations (Estonian Tuberculosis Registry).

2.6. Delay in diagnosis of pulmonary Tuberculosis

2.6.1. The Length of the Period of Delay

A delay in the diagnosis of TB increases the risk of both poor clinical outcome, including death, and transmission of TB. Understanding of factors that influence the delay is crucial for controlling TB [40, 118]. Delay between TB symptom onset and diagnosis, i.e., the total delay, has two constituent components: 1) patient delay, defined as the time interval between onset of the patient's first reported symptom and his/her referral to the physician and 2) HSD or doctor delay, which is an interval from the first medical visit to the date the TB diagnosis is done [5, 6, 32]. There is no general agreement for how long "acceptable" delays could be. An acceptable delay has been defined in two major ways: 1) either a panel of experts agrees on a reasonable period of time [37, 41, 119–121] or, alternatively, 2) the median and the 75th percentile of the duration of the delay is used [4, 6, 7, 33, 35, 40, 122]. Several panels of experts have determined that the maximum acceptable patient delay, HSD and total delay for smear-positive patients are 30 days, 10 days and 30–90 days, respectively [41, 119, 123]. It is recognized that much of the spread of TB may take place before the first contact with the medical care [34] and delays in diagnosing TB significantly increase the risk of TB transmission in the society. Most studies using the median patient delay have found medians ranging between 0.3–8 weeks, being 0.3 weeks in Gambia [7], 1.5 weeks in Auckland [25] and 2 weeks in Japan, Spain, Malaysia, Botswana and South India [4, 32, 36, 112, 124, 125]. 25-day and a 32-day median patient delay were reported in New York City [39] and in Maryland, U.S [26], respectively. The longest periods of patient delay has been reported in Tanzania, where the median patient delay was 120 days [41]. Little research has concentrated on examining patient delay and health care related delay in the countries of Eastern Europe and the former USSR. According to a recent study, the median patient delay in Kiev City, Ukraine, was 30 days [126].

In previous studies, where both smear-positive and smear-negative patients with pulmonary TB were analysed, HSD has been reported from 19.6 days to 56 days [7, 11, 33, 127]. In sputum smear-positive patients, HSD has been 2–25 days [5, 32, 37, 41, 121].

In European countries with stabile evolution of the social system during many decades, HSD has been documented to vary, being 5 weeks in London [128] and 6 days in Spain [122]. As mentioned, there are no studies on HSD in the countries of Eastern Europe and the former USSR.

Finally, it is important to mention that the delay in the diagnosis of pulmonary TB appears to be neither a single cause nor a result of the high prevalence of TB in the community since considerable delays have been described in both high- and low-prevalence countries [33].

2.6.2. Risk Factors for Delay

Timely diagnosis of active TB is particularly crucial to minimize disease transmission, but also morbidity and mortality in the community, as well within health care facilities [25]. To analyse the risk factors behind the delays, different methods have been used for the data collection. 1) All necessary data can be extracted from very different databases [4, 129], 2) questionnaires have been created to obtain data by interviewing the study population [38, 112] and 3) necessary data are obtained from the medical documentation at the health centres, TB cabinets, other ambulatory treatment facilities or from the hospital records of the clinics.

Risk Factors for Patient Delay

It is recognized that much of the spread of TB may take place before the first contact with the medical care and delays in diagnosing TB significantly increase the risk of TB transmission in the society [34]. Former studies indicate that a great variety of risk factors are associated with long patient delay including "barriers" in accessing health care such as living in rural areas [114], unemployment with missing health insurance [130], immigration and language barriers [39]. Almost all the studies have demonstrated that there are difficulties in accessing health care like living in rural areas [7, 35, 36]. The status of unemployment and missing health insurance as risk factors for patient delay have been described in many previous studies [34, 37, 126]. Prolonged patient delay has been associated with a great proportion of foreign-born people in the community, language difficulties and differences in the availability of medical care for these patients [34].

The advanced age and factors related to this are associated with prolonged patient delay [4, 7, 37, 39]. The effect of age on delay could be explained by the fact that in older patients, symptoms due to pre-existing comorbid illnesses can be mistaken as symptoms of TB when reporting the date of symptoms onset [11]. On the other hand, results of the studies from Southern Taiwan [131] and from Norway [132] demonstrated that prolonged patient delay could be associated with age less 60 or 65 years.

Results of studies from Nepal [121], as well as form United Kingdom [133], Queensland and Spain, [4, 121, 129, 133] demonstrated the longer period of patient delay in women. There is no general agreement about association of marital status and prolonged patient delay [37, 134]. Interestingly, both, unmarried [37] or married status [35], has been reported being risk factor for patient delay.

In the light of previous reports, patient delay is also associated with factors such as white race [40], non-white race [26], prior consultations with traditional

healers [36] and inadequate wisdom about [41]. Based on studies performed in such different sites as Ethiopia and Maryland, U.S., illiterate people and patients without at least elementary education have been found to be more prone to prolonged patient delay [7, 35]. Reports on the association between HIV-positivity and patient delay are varied. Patient delay has been associated with the presence [135, 136] or absence of HIV infection [37], some studies, however, show no significant association with HIV infection [36, 137]. The presence of some particular symptoms like fever, sweats and chest pain have been associated with shorter median patient delays [25]. Contradictory results, however, have been reported about associations between patient delay and haemoptysis among the symptoms. Patients seek medical care earlier when haemoptysis occurs among the symptoms [35], probably due to the impact of this shocking symptom on the patient or conversely, patients with haemoptysis had a longer delay [39, 131].

Risk Factors for Health System Delay

Numerous risk factors for prolonged HSD in TB have been identified in previous studies and they include severity of the disease, access to health services and expertise of the health care personnel. The speciality of the health care worker, whom the patient contacts first, is one of the most important factors, influencing the duration of HSD. Case detection is also dependent on operational effectiveness of the staff working at the health services [138]. In some studies, the type of medical facility has been the only factor having a significant association with health system delay [114]. The results are contradictory, but numerous studies highlight the fact that diagnosis of TB is often inadequate in private sector and the first visit made to the private clinic is the risk factor for prolonged HSD [112, 139–141]. Patient's first visit to the primary health centre or to the general practitioner has also an association with prolonged HSD [112, 123, 134]. On the contrary, patients presenting first to the Department of Emergency and Accident had shortest HSD [122]. Excessive waiting times for general practitioner and chest clinic appointments and results from investigations, as well as under-utilisation of all obligatory and cost-effective diagnostic methods clearly contribute to longer HSD.

The interviewing and examination of patients during the first visit should result in doctor's decision about the necessity of making chest X-ray, followed by other steps of the diagnosis. Missed chest radiograph at the first visit has been reported to result in longer delays in diagnosis [39, 131]. Importantly, enquiring TB patients about a history of TB in the family helps doctor to make the decision about chest X-ray [25]. The under-utilisation of smear microscopy, sputum culture or chest X-ray in the diagnosis of TB is associated with prolonged HSD [25, 116].

An atypical presentation of pulmonary TB may cause a delay in diagnosis [142–144]. Smear-negativity and absence of cough could be associated with so-called less extensive forms of TB (TB with lesions of less than 1 cm in diameter, e.g., focal TB), making diagnosis of which may need more time [6, 29, 62]. Contradictory results have been reported on association between the length of HSD and non-native nationality or unemployment. Interestingly, the status of unemployment and missing health insurance can be associated with shorter HSD [122], but with prolonged HSD as well [39, 145]. The remarkable proportion of immigrants among patients with pulmonary TB in Europe and higher index of suspicion of TB in individuals with respiratory symptoms, who are from countries with high prevalence of TB, could be an explanation for shorter patient delay in immigrants and in patients with non-native nationality [122, 132]. Prolonged HSD has been linked to an advanced age, it is associated with higher rates of co-morbidities in the elderly that mask the symptoms characteristic of TB and make differential diagnosis more difficult [122]. In an advanced age, even the clinical course of TB itself can differ from that usually expected. The complications of serious disorders like alcoholism, chronic renal failure, diabetes mellitus, neoplastic diseases and HIV infection can also easily modify the well-known clinical traits of TB and result in delays in diagnosis or misdiagnoses [78, 146]. Female TB patients experience significantly longer HSD than male patients by studies, carried out in Ghana [33], Vietnam [147, 148] and Nepal [33, 121, 147, 148]. The results of different studies on the association between HIV-positivity and the delay in diagnosis of TB are conflicting [29, 135].

2.7. The Strategy of Tuberculosis Management

2.7.1. Directly Observed Treatment Strategy

WHO policies [149–151] provide clear guidance on the management of all categories of TB [152]. To maximize TB control and research efforts, a clear strategic approach, DOTS has been developed and adopted in the 44th World Health

Assembly that met in May 1991 in Geneva, Switzerland. DOTS is the strategy, subsequently provided for effective TB control. The strategy comprised five essential elements. Two of them are technical: 1) case finding through bacteriological examinations of patients with respiratory symptoms attending primary health care units and 2) administration of short-course chemotherapy mostly under direct observation. The other three elements are managerial: 3) generating greater political commitment to mobilise sufficient resources for TB control, 4) securing a regular supply of anti-TB drugs and 5)

establishing a reliable information system to provide data for monitoring and assessing case finding and treatment activities [2, 13, 44, 46, 48]. Thanks to an aggressive campaign, the adoption of DOTS strategy quickly spread and soon it became one of the most well-known brands in the field of health [153]. DOTS was favoured by the demonstration that it was effective in achieving high cure rates [154, 155], in reducing TB mortality [156, 157] and incidence [158] in all countries, which adopted it [16, 44, 46]. However, DOTS has not appeared to be sufficient to control the epidemic in sub-Saharan Africa or Eastern Europe [16, 44, 46]. To address these challenges among many others to TB care and control, the WHO developed a broader approach that is embodied in the new Stop TB Strategy. The new strategy, while keeping DOTS as the first and foremost of its components has made explicit five additional components that must be implemented to reach the 2015 Millennium Development Goals relevant to TB [16, 159].

To manage MDR-TB with second-line drugs in resource-limited settings, DOTS-Plus was launched in 1999. Experts agreed on the need to face MDR-TB programmatically and. for this purpose, a formal WHO working group, named "DOTS-Plus for MDR-TB", was established. The Scientific Panel of the WHO Working Group on DOTS-Plus for MDR-TB produced the set of guidelines [160]. New guidelines, providing guidance on current best practice in management of drug resistant TB, were adopted in 2006 [161]. It is now clear that DOTS-Plus is an effective, feasible and cost-effective intervention, and the main challenges today are to expand drug resistance surveillance (DRS) and monitor drug resistance trends worldwide [1].

2.7.2. Global Plan to Stop TB

Stop TB is a global movement to accelerate social and political action to stop the spread of TB around the world. The Stop TB was established in 2000 to realize the goal of eliminating TB as a public health problem and, ultimately, to secure a world free of TB [162]. The first step was to develop the Global Plan to Stop TB (GPSTB) for 2001–2005, which consists of the various plans of the Partnership working groups and addresses the future work to expand DOTS, adapt it to the challenges of HIV and MDR-TB, develop new tools and strengthen the global movement to stop TB [163]. Most of the recommendations have materialised, including the establishment of a global alliance named the Stop TB Partnership [164], the creation of a Global Drug Facility, providing quality drugs against TB to countries in need [165–167]. The second GPSTB for 2006–2015 is intended to achieve its targets by 2015 [1]. The New Stop TB Strategy must be nurtured to maximize TB control and research efforts that will be conducive to a definitive success [59, 168]. GPSTB for 2006–2015 adopts the new WHO-recommended Stop TB Strategy, which provides a

comprehensive and inclusive vision for global TB control, incorporating human rights imperatives and health system strengthening.

WHO-Recommended Stop TB Strategy. Six Key Elements

1. Pursue quality DOTS expansion and enhancement, improving case-finding and cure through an effective patient-centred approach to reach all patients, especially the poor.
2. Address TB/HIV, MDR-TB and other challenges, by scaling up TB/HIV joint activities, DOTS-Plus and other relevant approaches.
3. Contribute to health system strengthening by collaborating with other health programmes and general services, for example in mobilizing the necessary human and financial resources for implementation and impact evaluation and in sharing and applying achievements of TB control.
4. Involve all care providers, public, nongovernmental and private, by scaling up approaches based on a public-private mix (PPM), to ensure adherence to the International Standards of TB Care.
5. Engage people with TB and affected communities to demand and contribute to, effective care. This will involve scaling up community TB care; creating demand through context-specific advocacy, communication and social mobilization; and supporting development of a patient's charter for the TB community.
6. Enable and promote research for the development of new drugs, diagnostics and vaccines. Research will also be needed to improve programme [1, 45].

2.7.3. The International Standards for Tuberculosis Care

Prompt, accurate diagnosis and effective treatment to cure are the core elements of TB control. The International Standards for Tuberculosis Care (ISTC) have been developed [16, 169]. ISTC document [170] has been developed to ensure quality of care across all providers. The ISTC is intended to facilitate the effective delivery of high-quality care for all patients regardless of age or gender, including the "complicated" cases, i.e., those who are sputum smear-negative, have extrapulmonary sites of disease and those who are affected by MDR-TB or co-infected with HIV. The document includes six standards for diagnosis, nine standards for treatment and two standards addressing public health responsibilities. The ISTC is fully consistent with WHO recommendations and with European Respiratory Society guidelines [10, 171]. The complete English versions of the ISTC and The Patients' Charter for Tuberculosis Care; outlining the rights and responsibilities of people with TB are available at http://www.worldcarecouncil.org.

Standard 1
All persons with otherwise unexplained productive cough lasting ≥2–3 weeks should be evaluated for TB.

Standard 2
All patients (adults, adolescents and children, who are capable of producing sputum) suspected of having pulmonary TB should have at least two and preferably three, sputum specimens obtained for microscopic examination. When possible, at least one early morning specimen should be obtained.

Standard 3
For all patients (adults, adolescents and children) suspected of having EPTB, appropriate specimens from the suspected sites of involvement should be obtained for microscopy and, where facilities and resources are available, for culture and histopathological examination.

Standard 4
All persons with chest radiographic findings suggestive of TB should have sputum specimens submitted for microbiological examination.

Standard 5
The diagnosis of sputum smear-negative pulmonary TB should be based on the following criteria: at least three negative sputum smears (including at least one early morning specimen); chest radiography findings consistent with TB; and lack of response to a trial of broad-spectrum antimicrobial agents. (Since fluoroquinolones are active against *Mycobacterium tuberculosis* complex and thus may cause transient improvement in persons with TB, they should be avoided). For such patients, if facilities are available, sputum cultures should be obtained. In persons with known or suspected HIV infection, the diagnostic evaluation should be expedited.

Standard 6
The diagnosis of intrathoracic pulmonary, pleural and mediastinal or hilar lymph node) TB in symptomatic children with negative sputum smears should be based on the finding of chest radiographic abnormalities consistent with TB and either a history of exposure to an infectious case or evidence of TB infection (positive tuberculin skin test or interferon gamma release assay). For such patients, if facilities for culture are available, sputum specimens should be obtained (by expectoration, gastric washings, or induced sputum) for culture [170].

3. OBJECTIVES OF THE STUDY

The studies were designed to characterize the epidemiological situation of TB in Estonia and to evaluate the process of diagnosis of TB with special regard to the risk factors for delay in the diagnosis in conditions of marked resurgence of TB.

The specific objectives were:

1) to analyse retrospectively the impact of the societal changes on the epidemiology of pulmonary and extrapulmonary TB between 1991 and 2000.
2) to analyse the distribution of extrapulmonary TB by age, gender, site and bacteriological confirmation.
3) to assess the length and determinants of patient and health system delay in pulmonary TB.
4) to evaluate the commonest symptoms and the first symptoms of pulmonary TB.
5) to analyse the interpretation of the symptoms and reactions on the symptoms, as well as on the TB diagnosis by the patients.

4. MATERIALS AND METHODS

4.1. Study Population, Study Area and Collection of Data

Table 1. Main characteristics of the studies performed

Study	Study subjects	No of subjects	Type of the study	Original papers
Epidemiology of TB in Estonia	Country-wide study during 1991–2000	5365	Descriptive epidemiology	I, II
Delay in diagnosis of TB	Six counties in Southern Estonia, 2002–2003	185	Risk factors for delay in diagnosis of pulmonary TB	III, IV

4.1.1. Epidemiological Situation of Tuberculosis in Estonia (I, II)

This study was designed as a country-wide retrospective study to include all incident cases of pulmonary TB and EPTB in Estonia from January 1991 to December 2000 (Table 1). The both demographic data and clinical information on the all new cases of active TB were analysed. In particular, data on the recorded incident cases of TB between 1991 and 1997 were obtained from the Department of Statistics of The Kivimäe Hospital, Tallinn, Estonia. Since 1997, the data was recorded in the Estonian Tuberculosis Registry. The data about birthplace for all patients separately for EPTB and pulmonary TB has been available since 1996.

Since 1998, pulmonary TB was defined as TB of the lung parenchyma and/or tracheo-bronchial tree and tuberculous pleurisy and intrathoracic lymph node TB were included as EPTB [2]. All data collected before 1998, were appropriately revised with this regard. All TB cases were registered according to one single site of affection. In case of the presence of a pulmonary manifestation, the patient was registered as having pulmonary TB regardless of the presence or absence of an extrapulmonary site according to the WHO guidelines [2]. Therefore, inclusion of patients having both EPTB and pulmonary TB into the analyses regarding EPTB was disabled.

The criteria for confirmation of diagnosis of TB were bacteriologic confirmation of *Mycobacterium tuberculosis* infection and/or histological analysis of the biopsy material. In cases of EPTB without bacteriological or histological confirmation, the diagnosis was based on clinical grounds, i.e., made by combinations of positive tuberculin skin test and recognition of signs and symptoms risen from involvement of particular organ or system. The data about drug sensitivity of *Mycobacterium tuberculosis* has been available from 1994.

4.1.2. The Delay in Diagnosis of Pulmonary Tuberculosis in Estonia (III, IV)

The study was conducted in six counties of Southern Estonia (Tartu, Võru, Põlva, Jõgeva, Valga and Viljandi county), representing 26% of the whole population of Estonia. The total population of Estonia was 1.4 million in January 2002 [172]. This population conformed the sample size (240 study subjects) that was calculated at 5% significance level and 80% power assuming to detect the statistically significant odds ratio (OR) of 2.10 (2-sided test, probability of exposure 0.5, ratio of delay group to non-delay group 1:1). In reality, regardless of the intent to involve all patients in the mentioned study area during the period 2002–2003, the total number of eligible patients was 187. Since two patients were lost to follow-up after diagnosis, the database was closed after enrolling 185 patients.

The inclusion criteria for the study population were:

- newly diagnosed pulmonary TB
- symptomatic patients
- age ≥16 years
- culture-positivity for *Mycobacterium tuberculosis* registration in the Estonian Tuberculosis Registry from 01.01.2002 to 31.12.2003.

The data were collected during patient interviews and supplemented from the respective medical records. The problem of insufficient information from doctors to the Estonian Tuberculosis Registry and the "loss of TB patients" was avoided by the system, according to which in addition to the doctors, also laboratories of mycobacteriology in Estonia have to send all information concerning smear and culture positive cases to the Estonian Tuberculosis Registry.

Interviews

The patients were interviewed face-to-face within 30 days of diagnosis in the language of the patient's preference, Estonian or Russian. Interviewer-administered questionnaire, modified with the authors' permission from a formerly implemented one [25] was used. As interviewers had a good command of Estonian and Russian, there was no need to use an interpreter.

Detailed data were collected on each patient to determine social and demographic variables, as well as the dates of onset of TB-related symptoms: cough, sputum production, haemoptysis, shortness of breath, chest pain, fever, sweats, fatigue, anorexia and weight loss. If the patient was able to report the week or month of onset of any of the symptoms, the last day of the week or the

15th day of the month under question was recorded as the onset, respectively. The date and specialty of the health care worker the patient contacted first were also registered. Health care workers were divided into 3 groups: pulmonologists, family doctors and other specialists. Other specialties included emergency department doctors, physicians of other specialties and nurses.

The dates of the first chest X-ray and the data about acid-fast bacilli (AFB) smear as well as the results of HIV-testing, routinely made after the TB diagnosis, were obtained from the medical records. The presence of TB contacts was recorded if reported by the patient or if there was an appropriate statement in the patient's medical record.

Potential reasons for care-seeking delay were elucidated by specific questions about patient's possible explanations of arisen symptoms, certain specific remedial actions they had taken for the symptoms prior to seeking an advice of a doctor and potential other reasons for postponing medical consultation.

The information about history of TB contacts, as well as the dates of the first chest X-ray and the data about AFB smear and the results of HIV-testing were registered.

Interpretation of the Delays

Patient delay was defined as the interval in days from the date of onset of whatever first reported symptom to the date of the patient's first visit to the health care provider [5, 6]. HSD was defined as the interval in days from the date when a medical provider was first contacted by the patient to the date the TB diagnosis was made [5–7]. The median and the 75^{th} percentile of the patient delay and HSD were calculated in days.

The categories "prolonged patient delay" [11] and "extreme patient delay" [4] were used, defined as greater than the median and greater than the 75^{th} percentile of the length of the patient delay, respectively. Analogously, "prolonged HSD" and "extreme HSD" were used, defined as delays greater than the median and greater than the 75^{th} percentile of the length of the HSD delay, respectively. To analyse the impact of each particular symptom on the patient delay, median of the interval from the onset of the symptom to the first medical visit were calculated.

4.2. Statistical Analysis

4.2.1. Epidemiological Situation of Tuberculosis (I, II)

For the analysis of the epidemiology of TB, crude and age-specific incidence rates were computed for TB using relevant population data. The chi square test for ratio's trend was applied to analyse the change of EPTB incidence compared to that of pulmonary TB, as well as to analyse the distribution of different sites of EPTB over the period 1991–2000. This test was also used to analyse the age trends in the distribution of sites of EPTB. The number of incident cases was used as input data in all analyses. The differences between EPTB and pulmonary TB populations for the proportions of bacteriological confirmation and multidrug resistance were tested with use of the chi square fourfold table test. p-values below 0.05 were accepted as indicative of statistical significance.

4.2.2. Risk Factors for Delay in Diagnosis of Pulmonary Tuberculosis (III, IV)

Logistic regression with two cut-off points (median and 75th percentile) was used to estimate the association of potential risk factors for prolonged patient delay and prolonged HSD, as well as for extreme patient delay and extreme HSD. Odds ratios (OR) and associated 95% confidence intervals (95% CI) were calculated by logistic regression model and used as measures of strength of association between the outcome variables and their predictors. For the analysis of the risk factors for HSD, each OR was adjusted for all other characteristics within two models: one consisting of demographic and another of medical variables.

The lack of health insurance as a risk factor for HSD was calculated additionally, OR was adjusted for gender, age, presence of cough among symptoms, speciality of the doctor the patient contacted first, having X-ray during first visit, sputum smear status and history of TB contacts.

The analysis was performed using Stata 8.0 (StataCorp. 2003. Stata Statistical Software, Release 8.0, Stata Corporation, College Station, TX, USA).

4.3. Ethics

All study protocols were approved by the Ethics Committee on Human Research at the University of Tartu. Written informed consent was obtained from the patients for the interview and following data analysis. There were no refusals and nobody drew back his or her informed consent during the course of the study.

5. RESULTS

5.1. The Epidemiological Situation of Tuberculosis in Estonia 1991–2000 (I, II)

5.1.1. Incidence rates of Pulmonary and Ekstrapulmonary Tuberculosis

Out of the 5365 new cases of TB, 4743 were pulmonary and 622 were extrapulmonary in Estonia during the 10-year period 1991–2000. Although the total number of all cases of TB increased from 336 in 1991 to 689 in 1998, the situation has stabilized since 1999. The incidence of new cases of TB in Estonia increased from 21.5/100 000 in 1991 to 44.6/100 000 in 2000. The incidence of EPTB increased only from 3.6 in 1991 to 4.7 in 2000 (Table 2). The total number of pulmonary TB cases increased from 279 in 1991 to 577 in 2000. Due to the number of EPTB remained constant, being 57 and 65 in 1991 and 2000, respectively, the proportion of EPTB among overall TB steadily decreased from 17.0% in 1991 to 10.1% in 2000. As a result, the change in the number of EPTB cases is significantly less that that of pulmonary TB ($p<0.05$). In 1991–1995, the proportion of EPTB was significantly higher than during the second half of the decade 1996–2000 ($p<0.05$).

Out of all EPTB cases, 54% were male and 46% female (male-female ratio 1.16:1). The distribution of EPTB cases by gender significantly differed from that in pulmonary TB (male-female ratio 2.62:1) ($p<0.05$).

In 1996–2000, 45 (13.7%) of all EPTB patients (n = 328) and 632 (21.8%) of all pulmonary TB cases (n = 2900) were born outside of Estonia. Eight (2.4%) of the EPTB patients and 49 (1.7%) of the pulmonary TB patients had lived in Estonia for less than 5 years. Forty (88.9%) of all foreign-born EPTB patients and, for comparison, 535 (84.7%) of all foreign-born pulmonary TB patients were of Russian origin.

By 2000, only three patients with pulmonary TB were found to be infected with HIV (one case in 1997, one in 1999 and one in 2000).

Table 2. New cases of overall active tuberculosis and extrapulmonary tuberculosis in Estonia, 1991–2000

Year	All TB, total number	All TB, incidence rate per 100 000	EPTB, total number[a,b]	EPTB, incidence rate per 100 000	Percentage of EPTB cases among all TB cases	All TB among children + adolescents, (total number)
1991	336	21.5	57	3.6	17.0	5+5
1992	328	21.2	46	3.0	14.0	4+3
1993	441	29.1	59	3.9	13.4	4+2
1994	518	34.6	66	4.4	12.7	9+4
1995	516	34.8	66	4.5	12.8	18+12
1991–1995	2139	28.2	294	3.9	13.8	40+26
1996	593	40.4	63	4.4	10.6	16+12
1997	660	45.3	74	5.2	11.2	27+4
1998	689	47.5	65	4.6	9.4	10+9
1999	642	44.5	61	4.4	9.5	14+9
2000	642	44.6	65	4.7	10.1	19+12
1996–2000	3226	44.5	328	4.6	10.2	86+46
Total	5365	36.2	622	4.2	12.1	126+72

[a]The change in the number of EPTB cases is significantly less that that of pulmonary TB ($p<0.05$).
[b]In 1991–1995, the proportion of EPTB was significantly higher than during the second half of the decade 1996–2000 ($p<0.05$).

5.1.2. Distribution of Sites of Extrapulmonary Tuberculosis

Of the 622 EPTB cases, 210 (33.8%) were pleural, 128 (20.6%) were bone and joint, and 126 (20.3%) were lymph node TB (Table 3). Out of the latter, 73 patients had the disease in their intrathoracic lymph nodes. In contrast to other sites of EPTB, the annual number of cases of intrathoracic lymph node TB increased significantly during the 10-year period ($p<0.05$). A number of other sites of EPTB, including TB of skin, eye, liver and intestines, showed a significant decrease ($p<0.05$), whereas the annual number of cases of osteoarticular and urogenital TB remained unchanged over the 1991–2000 period. No cases of miliary TB were diagnosed in Estonia during this period.

Table 3. Number of new cases of extrapulmonary tuberculosis by site in Estonia, 1991–2000

Year	Pleural	Oste-articular	Uro-genital	Super-ficial lymph nodes	Intra-thoracic lymph nodes	Central nervous system	Other
1991	18	11	15	7	2	4	0
1992	14	11	8	2	3	2	6
1993	21	19	6	2	3	1	7
1994	22	16	10	9	4	1	4
1995	18	15	11	6	12	2	2
1996	17	14	14	4	13	0	1
1997	20	10	15	9	17	1	2
1998	27	8	14	4	7	1	4
1999	21	14	12	5	7	1	1
2000	32	10	8	5	5	2	3
Total	210	128	113	53	73	15	30
(%)[a]	33.8%	20.6%	18.2%	8.5%	11.7%	2.4%	4.8%
p-value[b]	0.15	0.27	0.35	0.27	<0.05	0.46	<0.05

[a]Percentage among all cases of EPTB
[b]p-values indicate the significance of the trends over time attributed to particular sites of EPTB in relation to the number of overall EPTB

5.1.3. Distribution of Extrapulmonary Sites of Tuberculosis by Age and Gender

The proportion of EPTB out of all TB cases decreased significantly with increasing age, being 66%, 35% and 10% for patients under the age of 15, for adolescents and for adults, respectively ($p<0.05$) (Table 4). The most common site of EPTB in children was the intrathoracic lymph node (80.7%), whereas osteoarticular TB accounted for only 7.2% and pleural TB for 3.6% of EPTB cases. Among adolescents and adults, pleural TB predominated as the main site of EPTB in 40.0% and 38.3% of cases, respectively. Of all the EPTB cases, the proportion affecting the intrathoracic lymph nodes decreased significantly with age, accounting for 80.7% in children and 16% in adolescents, but only for 0.4% in adults ($p<0.05$). In contrast, the proportions of urogenital TB and osteoarticular TB increased noticeably with age ($p<0.05$).

Table 4. Age distribution of patients with overall tuberculosis and extrapulmonary tuberculosis by site in Estonia, 1991–2000

	0–14 yr No (%)	15– 17 yr No (%)	≥18 yr No (%)	p-value[a]
All TB	126	72	5167	
EPTB	83 (100)	25 (100)	514 (100)	<0.05
Intrathoracic lymph node	67 (80.7)	4 (16.0)	2 (0.4)	<0.05
Pleural	3 (3.6)	10 (40.0)	197 (38.3)	<0.05
Superficial lymph node	5 (6.0)	4 (16.0)	44 (8.6)	0.29
Osteoarticular	6 (7.2)	4 (16.0)	118 (23.0)	<0.05
Urogenital	1 (1.2)	2 (8.0)	110 (21.4)	<0.05
Central nervous system	0	0	15 (2.9)	0.60
Skin	0	0	10 (1.9)	0.36
Eye	0	0	13 (2.5)	0.36
Other sites	1 (1.2)	1 (4.0)	5 (1.0)	0.37

[a]p-values indicate the significance of age trends attributed to numbers of patients with particular EPTB.

In both male and female patients, pleural, osteoarticular, genitourinary and lymphatic TB accounted for more than 90% of EPTB (Table 5). The only major gender difference was apparent in lymphatic TB, the third leading site in males and the second in females after pleurisy, which was the most frequent site in both genders. More interestingly, superficial lymph node TB, but not intrathoracic lymph node involvement had a strong female predominance.

Table 5. Distribution of sites of extrapulmonary tuberculosis by gender, 1991–2000

Variables	Pleural	Osteo-articular	Super-ficial lymph nodes	Intra-thoracic lymph nodes	Uro-genital	Central Nervous System	Other
Total EPTB cases, %							
Male gender	37.1	21.6	4.8	13.5	16.2	2.7	4.2
Female gender	29.9	19.4	12.8	9.7	20.5	2.1	5.6

5.1.4. Distribution of Forms of Pulmonary Tuberculosis

Analysis of forms of pulmonary TB demonstrated that the proportion of cavitary forms was quite constant throughout the study, being around 65% of all pulmonary cases (Table 6). In contrast, the number of less extensive forms of pulmonary TB decreased from 33 (11.8%) in 1991 to 14 (2.4%) in 2000.

Table 6. Cavitary forms, less extensive forms and bacteriological confirmation of the diagnosis of pulmonary tuberculosis in Estonia, 1991–2000

Year	Pulmonary TB Total No	Cavitary forms No (%)	Less extensive forms (infiltrate <1cm), No (%)	Culture positive No (%)
1991	279	183 (65.6)	33 (11.8)	199 (71.3)
1992	282	188 (66.7)	41 (14.5)	188 (66.7)
1993	382	282 (73.8)	39 (10.2)	263 (68.8)
1994	452	318 (70.4)	43 (9.5)	303 (67.0)
1995	450	340 (75.6)	55 (12.2)	330 (73.3)
1996	530	356 (67.1)	74 (13.9)	382 (72.0)
1997	586	356 (60.8)	55 (9.4)	389 (66.4)
1998	626	402 (64.2)	47 (7.5)	433 (69.2)
1999	581	452 (77.8)	33 (5.7)	425 (73.1)
2000	577	474 (82.1)	14 (2.4)	410 (71.8)

5.1.5. Bacteriological and Histopathological Confirmation of the Diagnosis

The percentage of culture positive cases among all cases of EPTB was 39.7 in 1996 and 40.0 in 2000. For comparison, in pulmonary TB, the rate of confirmation was significantly higher ($p<0.05$) (Table 6). Analysis of the rate of bacteriological confirmation for sites of EPTB revealed that in urogenital TB, the rate ranged widely, being 71.4% in 1996, 26.7% in 1997, 85.7% in 1998, 66.6% in 1999 and 50% in 2000. Surprisingly, the proportion of confirmed diagnoses of pleural TB decreased from 70.6% in 1996 to 56.3% in 2000. For other sites of EPTB, the confirmation rate was lower, for instance, it was close to zero in intrathoracic lymph node TB (Table 7).

Multidrug Resistance among Extrapulmonary and Pulmonary Tuberculosis

In bacteriologically confirmed EPTB, multidrug resistance was reported in overall six cases: three cases (9.7%) in 1998, two cases (8%) in 1999 and one case (3.8%) in 2000. This proportion, although being obviously lower than that for pulmonary TB (11.1% in 1997, 14.1% in 1998, 17.1% in 1999 and 12.0% in 2000), did not differ statistically from the latter ($p>0.05$).

Table 7. Bacteriological and/or histopathological confirmation (%) of the diagnosis of extrapulmonary tuberculosis by site in Estonia, 1996–2000

Year	EPTB total	Culture positive cases	Pleural	Osteo-articular	Uro-genital	Superficial lymph nodes	Intrathoracic lymph nodes
	No	No (%)	No (%)	No (%)	No (%)	No (%)	No (%)
1996	63	25 (39.7)	12 (70.6)	0	10 (71.4)	3 (75.0)	0
1997	74	24 (32.4)	13 (65.0)	0	4 (26.7)	5 (55.0)	0
1998	65	31 (47.7)	17 (63.0)	0	12 (85.7)	2 (50.0)	0
1999	61	25 (41.0)	10 (47.6)	3 (21.4)	8 (66.6)	3 (60.0)	0
2000	65	26 (40.0)	18 (56.3)	2 (20.0)	4 (50.0)	0	1 (20.0)

5.2. The Delay in Diagnosis of Pulmonary Tuberculosis

5.2.1. Patient Characteristics (III, IV)

Of the 303 cases of TB recorded in the Southern Estonia during the study period from January 2002 to December 2003, 48 relapses, 33 culture negative cases, 25 cases with extrapulmonary TB, nine patients without symptoms and one child were excluded according to the protocol. Among the 187 eligible patients, 185 were enrolled into the study (Table 8) and two were lost to follow-up immediately after the diagnosis. Although 16.8% of the patients were foreign-born and 26.5% were ethnically non-Estonians, all patients had lived in Estonia for more than 10 years and only three patients (1.6%) had lived in Estonia for less than 20 years.

Almost half of patients (49.7%) declared about a history of TB contacts and 55.1% were smear-positive at the moment of the diagnosis (Table 9). Also, 175 patients (94.6%) were tested to be negative for HIV, seven patients (3.8%) were not tested and for the rest three patients (1.6%), the testing status was not known.

Table 8. Distribution of patients with culture-proven pulmonary tuberculosis (n = 185) by socio-demographic characteristics, six counties of Southern Estonia, 2002–2003

Characteristic	No (%)
Gender	
Male	126 (68.1)
Female	59 (31.9)
Age at diagnosis, yr	
≤29	20 (10.8)
30–39	33 (17.8)
40–49	54 (29.2)
50–59	35 (18.9)
60–69	20 (10.8)
≥70	23 12.4)
Ethnicity	
Estonian	136 (73.5)
Non-Estonian	49 (26.5)
Place of residence	
Urban	118 (63.8)
Rural	67 (36.2)
Education	
Basic	89 (48.1)
Secondary	35 (47.0)
University	9 (4.9)
Marital status	
Married/cohabiting	79 (42.7)
Single	39 (21.1)
Divorced	43 (23.2)
Widowed	24 (13.0)
Activity	
Employed	39 (21.1)
Retired	39 (21.1)
Disabled	21 (11.4)
Student	4 (2.2)
Housewife	1 (0.5)
Unemployed	81 (43.8)
Health insurance	
Yes	120 (64.9)
No	65 (35.1)

Table 9. Distribution of patients with culture-proven pulmonary tuberculosis (n = 185) by medical characteristics, six counties of Southern Estonia, 2002–2003

Characteristic	No (%)
Patient sought help first	
Pulmonologist	28 (15.1)
Family doctor	103 (55.7)
Other specialties[a]	54 (29.2)
Sputum smear status	
Smear positive	102 (55.1)
Smear negative	83 (44.9)
Cough among symptoms	
Yes	134 (72.4)
No	51 (27.6)
History of TB contacts	
Yes	92 (49.7)
No	93 (50.3)
X-ray at the first visit	
Yes	97 (52.4)
No	88 (47.6)
TB with destruction	
Yes	147 (79.5)
No	38 (20.5)
Drug abuse	
Yes	2 (1.1)
No	183 (98.9)
HIV status	
Negative	175 (94.6)
Positive	0
Unknown	10 (5.4)

[a]Other specialties included emergency department doctors, physicians of other specialties and nurses.

5.2.2. Symptoms of Pulmonary Tuberculosis and Health Care Seeking Behaviour (III)

The average number of symptoms per patient was 5.5. Fatigue, cough and fever were the three leading symptoms reported by the patients during their illness. Also, these symptoms were reported by the patients as the most often patients' first symptoms (Table 10). Roughly half of the patients, 101 (54.6%) thought that their symptoms were caused by common cold, 14 patients (7.6%) were of the opinion that the symptoms had been caused by common tiredness and seven patients (3.8%) believed in an exacerbation of a pre-existing chronic lung disease. Only 27 patients (14.6%) declared their suspicion of being ill with TB. A total of 161 patients (87.0%) actively sought medical care because of their

symptoms. Of those, 136 patients (84.5%) had symptoms referring to TB and 25 (15.5%) had symptoms, which were more likely to be associated with other illnesses. The rest of the patients, although symptomatic, either were obliged to contact the health care provider for routine control (17 patients, 9.2%) or were investigated as contacts of TB smear-positive cases (7 patients, 3.8%).

In 103 cases (55.7%), medical assistance was first sought from a general practitioner and in 28 cases (15.1%), from a pulmonary specialist. In 49 cases (26.5%), the patients first turned to an emergency department or TB was discovered by doctors of other specialties. In five cases (2.7%), the patients first contacted a nurse. No consultations with private doctors and traditional healers were reported.

Table 10. Symptoms of patients with culture-proven pulmonary tuberculosis (n = 185), six counties of Southern Estonia, 2002–2003

Symptom	Occurred No (%)	Noticed first[a] No (%)
Fatigue	148 (80.0)	71 (38.4)
Cough	133 (71.9)	73 (39.5)
Fever	128 (69.2)	31 (16.8)
Sputum production	89 (48.1)	27 (14.6)
Weight loss	86 (46.5)	27 (14.6)
Sweats	79 (42.7)	22 (11.9)
Chest pain	48 (25.9)	9 (4.9)
Anorexia	48 (25.9)	9 (4.9)
Shortness of breath	52 (28.1)	7 (3.8)
Haemoptysis	19 (10.3)	4 (2.2)

[a]More than one symptom could be noticed first (at the same time).

5.2.3. Patient Delay and Risk Factors for Patient Delay (III)

The median and 75th percentile of the period between onset of whatever first symptom and first medical visit were 79 and 140 days, respectively (range 0–580 days). Male gender and rural residence were the factors significantly associated with prolonged patient delay, whereas male gender alone was significantly related to extreme patient delay (Tables 11 and 12). Neither education, ethnicity, age, marital status nor unemployment had a significant impact on any aspect of the patient delay.

Analysis of the patient delay by different first symptoms revealed that the median patient delay was shortest when the first symptom was fever and greatest when it was haemoptysis, followed by cough and anorexia (Figure 1).

Table 11. Odds ratios (OR) and 95% confidence intervals (CI) for prolonged patient delay in newly detected symptomatic patients with pulmonary tuberculosis, Southern Estonia, 2002–2003

Characteristic	No (%) with longer than median delay	Crude OR (95% CI)	p-value	Adjusted OR[a] (95% CI)	p-value
Gender					
Female	21 (35.6)	1.0		1.0	
Male	80 (63.5)	2.26 (1.19–4.28)*	0.02	2.12 (1.06–4.23)*	0.02
Age					
≤39	26 (49.1)	1.0		1.0	
40–59	49 (55.1)	1.27 (0.64–2.51)	0.49	0.79 (0.37–1.70)	0.55
≥60	16 (37.2)	0.62 (0.27–1.40)	0.25	0.53 (0.21–1.36)	0.19
Ethnicity					
Estonian	63 (46.3)	1.0		1.0	
Non-Estonian	28 (57.1)	1.54 (0.80–2.98)	0.19	1.78 (0.85–3.72)	0.13
Marital status					
Married/ Cohabiting	31 (39.2)	1.0		1.0	
Single/Divor-ced/Widowed	60 (56.6)	2.02 (1.12–3.65)*	0.02	1.90 (0.99–3.66)	0.05
Education					
Secondary/ University	47 (49.0)	1.0		1.0	
Basic	44 (49.5)	1.02 (0.57–1.82)	0.95	0.92 (0.49–1.75)	0.80
Place of residence					
Urban	53 (44.9)	1.0		1.0	
Rural	38 (56.7)	1.61 (0.88–2.94)	0.12	2.08 (1.06–4.08)*	0.03
Activity					
Employed/ Retired/Other	42 (40.4)	1.0		1.0	
Unemployed	49 (60.5)	2.26 (1.25–4.09)*	0.007	1.39 (0.67–2.87)	0.38

[a] Each OR was adjusted for all other characteristics in the table.
*Significant change

Table 12. Odds ratios (OR) and 95% confidence intervals (CI) for extreme patient delay in newly detected symptomatic patients with pulmonary tuberculosis, Southern Estonia, 2002–2003

Characteristic	No (%) with longer than median delay	Crude OR (95% CI)	p-value	Adjusted OR[a] (95% CI)	p-value
Gender					
Female	19 (32.2)	1.0		1.0	
Male	78 (61.9)	3.33 (1.39–7.99)*	<0.001	3.28 (1.30–8.26)*	<0.001
Age					
≤39	15 (28.3)	1.0		1.0	
40–59	25 (28.1)	0.99 (0.46–2.11)	0.98	0.59 (0.25–1.36)	0.21
≥60	6 (13.9)	0.41 (0.14–1.17)	0.1	0.46 (0.14–1.50)	0.19
Ethnicity					
Estonian	30 (22.1)	1.0		1.0	
Non-Estonian	16 (32.7)	1.71 (0.83–3.53)	0.14	1.86 (0.82–4.21)	0.14
Marital status					
Married/ Cohabiting	16 (20.3)	1.0		1.0	
Single/Divor-ced/Widowed	30 (28.3)	1.55 (0.78–3.11)	0.21	1.22 (0.57–2.63)	0.61
Education					
Secondary/ University	26 (27.1)	1.0		1.0	
Basic	20 (22.5)	0.78 (0.40–1.53)	0.47	0.75 (0.36–1.57)	0.45
Place of residence					
Urban	28 (23.7)	1.0		1.0	
Rural	18 (26.8)	1.18 (0.59–2.35)	0.64	1.46 (0.68–3.10)	0.33
Activity					
Employed/ Retired/Other	17 (16.4)	1.0		1.0	
Unemployed	29 (35.8)	2.85 (1.43–5.69)*	0.003	1.99 (0.86–4.60)	0.11

[a]Each OR was adjusted for all other characteristics in the table.
*Significant change

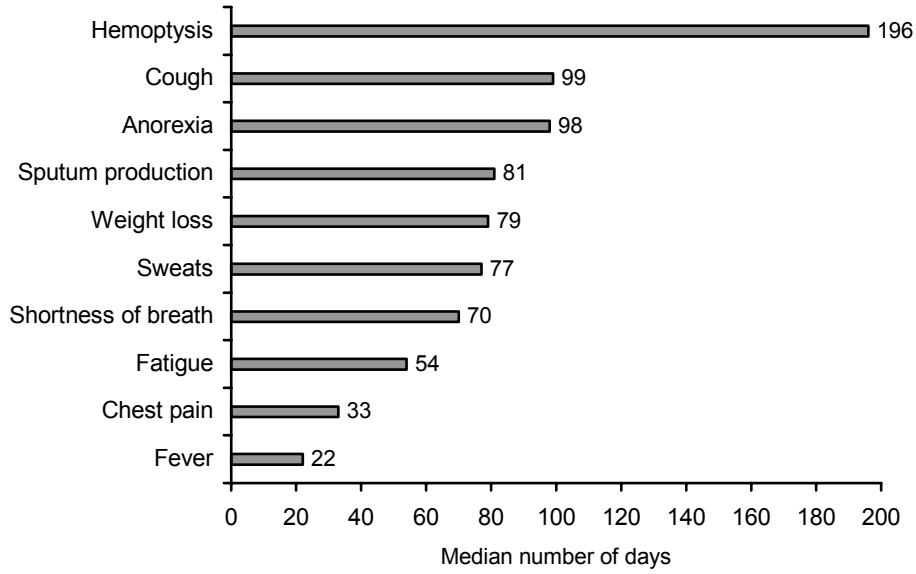

Figure 1. The length of patient delay (median number of days) by first symptoms in patients with symptomatic culture-proven pulmonary tuberculosis (n = 185), six counties of Southern Estonia, 2002–2003

5.2.4. Health System Delay and Risk Factors for Health System Delay (IV)

Median and 75th percentile of the period between the date of the first medical visit and the date of diagnosis of TB were 19 and 40 days, respectively. Multivariate analysis showed that the factors significantly associated with prolonged HSD were smear negativity, absence of cough among the symptoms, missing X-ray during the first visit (Table 13). Factors associated with extreme HSD were smear negativity, missing X-ray during the first visit, age over 60 years (Table 14). Prolonged HSD delay was shorter in non-Estonians (Table 13), but extreme HSD was shorter in non-Estonians and in unemployed patients (Table 14). Missing health insurance was associated with significantly shorter prolonged and extreme HSD (Tables 15 and 16). Neither prolonged nor extreme HSD were associated with patient's gender, marital status, education, having history of TB contacts and specialty of the health care worker the patient contacted first.

Table 13. Risk factors for prolonged health system delay in newly detected symptomatic patients with pulmonary tuberculosis, Southern Estonia, 2002–2003

Characteristic	No (%) with longer than median delay	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Demographic variables[a]					
Gender					
Male	57 (45.2)	1.0		1.0	
Female	35 (59.3)	1.77 (0.94–3.30)	0.076	1.46 (0.72–2.97)	0.30
Age					
≤39	29 (54.7)	1.0		1.0	
40–59	36 (40.5)	0.56 (0.28–1.12)	0.100	0.89 (0.42–1.93)	0.78
≥60	27 (62.8)	1.40 (0.61–3.18)	0.43	1.85 (0.70–4.89)	0.22
Marital status					
Married/Cohabiting	47 (59.5)	1.0		1.0	
Single/Divorced/ Widowed	45 (42.5)	0.50 (0.28–0.91)	0.02	0.63 (0.33–1.23)	0.18
Education					
Secondary/ University	52 (52.2)	1.0			
Basic	40 (44.9)	0.69 (0.39–1.23)	0.21	0.64 (0.33–1.23)	0.18
Place of residence					
Urban	60 (50.9)	1.0		1.0	
Rural	32 (47.8)	0.88 (0.49–1.61)	0.69	0.69 (0.35–1.36)	0.28
Activity					
Employed/ Retired/Other	64 (61.5)	1.0		1.0	
Unemployed	28 (34.6)	0.33 (0.18–0.60)*	<0.001	0.58 (0.28–1.19)	0.14
Ethnicity					
Estonian	78 (57.4)	1.0		1.0	
Non-Estonian	14 (28.6)	0.30 (0.15–0.60)*	0.001	0.28 (0.13–0.60)*	0.001

Table 13. Continuation

Characteristic	No (%) with longer than median delay	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Medical variables[b]					
First visit to					
Pulmonologist	11 (39.3)	1.0		1.0	
Family doctor	58 (56.3)	1.99 (0.85–4.67)	0.11	1.56 (0.55–4.43)	0.40
Other specialties[c]	23 (42.6)	1.15 (0.45–2.91)	0.77	0.70 (0.20–2.42)	0.58
Cough among symptoms					
Yes	58 (43.3)	1.0		1.0	
No	34 (66.7)	2.62 (1.33–5.15)*	0.005	2.23 (1.06–4.71)*	0.03
X-ray at the first visit					
Yes	46 (47.4)	1.0		1.0	
No	46 (52.3)	1.21 (0.68–2.16)	0.51	2.36 (1.07–5.18)*	0.03
Sputum smear status					
Smear positive	38 (37.3)	1.0		1.0	
Smear negative	54 (65.1)	3.14 (1.71–5.74)*	<0.001	3.68 (1.82–7.43)*	<0.001
History of TB contacts					
Yes	43 (46.7)	1.0		1.0	
No	49 (52.7)	1.27 (0.71–2.26)	0.42	1.12 (0.56–2.24)	0.75

[a]Each OR was adjusted for other demographic variables
[b]Each OR was adjusted for medical variables, but also for gender and age (not shown)
[c]Other specialties included emergency department doctors, physicians of other specialties and nurses.
*Significant change

Table 14. Risk factors for extreme health system delay in newly detected symptomatic patients with pulmonary tuberculosis, Southern Estonia, 2002–2003

Characteristic	No (%) with longer than median delay	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Demographic variables[a]					
Gender					
Male	30 (23.8)	1.0		1.0	
Female	15 (25.4)	1.09 (0.53–2.23)	0.81	0.95 (0.42–2.18)	0.91
Age					
≤39	8 (15.1)	1.0		1.0	
40–59	18 (20.2)	1.43 (0.57–3.55)	0.45	2.29 (0.83–6.34)	0.11
≥60	19 (44.2)	4.45 (1.70–11.67)*	0.002	4.67 (1.57–13.87)*	0.006
Marital status					
Married/ Cohabiting	24 (30.4)	1.0		1.0	
Single/Divorced /Widowed	21 (19.8)	0.57 (0.29–1.11)	0.099	0.57 (0.26–1.26)	0.16
Education					
Secondary/ University	20 (20.8)	1.0		1.0	
Basic	25 (28.1)	1.48 (0.76–2.92)	0.25	1.37 (0.63–3.0)	0.43
Place of residence					
Urban	28 (27.3)	1.0		1.0	
Rural	17 (25.4)	1.09 (0.55–2.19)	0.80	0.76 (0.35–1.69)	0.51
Activity					
Employed/ Retired/Other	36 (43.6)	1.0		1.0	
Unemployed	9 (11.1)	0.24 (0.11–0.53)*	<0.001	0.37 (0.14–0.94)*	0.037
Ethnicity					
Estonian	40 (29.4)	1.0		1.0	
Non-Estonian	5 (10.2)	0.27 (0.10–0.74)*	0.011	0.25 (0.08–0.72)*	0.010

Table 14. Continuation

Characteristic	No (%) with longer than median delay	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Medical variables[b]					
First visit to					
Pulmonologist	3 (10.7)	1.0		1.0	
Family doctor	30 (29.1)	3.42 (0.96–12.2)	0.06	2.06 (0.46–9.22)	0.34
Other specialties[‡]	12 (22.2)	2.38 (0.61–9.26)	0.21	0.73 (0.14–3.87)	0.71
Cough among symptoms					
Yes	31 (23.1)	1.0		1.0	
No	14 (27.5)	1.26 (0.60–2.62)	0.54	1.14 (0.49–2.61)	0.76
X-ray at the first visit					
Yes	16 (16.5)	1.0		1.0	
No	29 (32.9)	2.49 (1.24–4.99)*	0.01	3.39 (1.42–8.10)*	0.006
Sputum smear status					
Smear positive	21 (20.6)	1.0		1.0	
Smear negative	24 (28.9)	1.57 (0.80–3.08)	0.19	2.24 (1.02–4.93)*	0.045
History of TB contacts					
Yes	19 (20.7)	1.0		1.0	
No	26 (28.0)	1.49 (0.76–2.94)	0.25	1.26 (0.57–2.79)	0.57

[a]Each OR was adjusted for other demographic variables

[c]Other specialties included emergency department doctors, physicians of other specialties and nurses.

*Significant change

Table 15. Missing health insurance as a risk factor for prolonged health system delay in newly detected symptomatic patients with pulmonary tuberculosis, Southern Estonia, 2002–2003

Health insurance	Crude OR[a] (95% CI)	p-value	Adjusted OR[a] (95% CI)	p-value
No	1.0		1.0	
Yes	3.04 (1.61–5.73)	0.001	2.55 (1.16 –5.60)*	0.02

[a]Each OR was adjusted for gender, age, having cough among symptoms, specialty of the doctor the patient contacted first, having X-ray during first visit, sputum smear status and history of TB contacts.
*Significant change

Table 16. Missing health insurance as risk factor for extreme health system delay in newly detected symptomatic patients with pulmonary tuberculosis, Southern Estonia, 2002–2003

Health insurance	Crude OR[a] (95% CI)	p-value	Adjusted OR[a] (95% CI)	p-value
No	1.0		1.0	
Yes	3.02 (1.61–5.73)	<0.001	5.40 (1.77 –16.44)*	0.003

[a]Each OR was adjusted for gender, age, having cough among symptoms, specialty of the doctor the patient contacted first, having X-ray during first visit, sputum smear status and history of TB contacts.
*Significant change

5.2.5. Patient, Health System and Total Delays

Medians and 75th percentiles of the total delay (the time interval between the occurrence of the first symptoms and the date of the diagnosis) were 119 and 187 days, respectively (Table 17).

Table 17. Medians and 75th percentiles of the patient delay, health system delay and total delay (in days) among newly detected symptomatic patients with pulmonary tuberculosis, Southern Estonia, 2002–2003

	Patient delay	HSD	Total delay	Patient delay	HSD	Total delay
	Median			75th percentile		
Total	79	19	119	140	40	187

5.2.6. Remedial Actions Undertaken by the Patients Prior to Contacting Health Care (III)

Almost all patients (99.5%) claimed to have undertaken at least one action due to their symptoms: a total of 133 patients (71.9%) waited to get better on their own, 86 (46.5%) began to have more rest, 50 (27.0%) used medicines accessible without a doctor's prescription, 16 (8.6%) reduced smoking and 29 (15.7%) and 4 (2.2%) increased or reduced alcohol intake, respectively.

5.2.7. Reasons to Postpone Seeking for Medical Care by the Patients (III)

Most of the patients (165 or 89.2%) found at least one reason for postponing care seeking (Table 18), whereas some patients presented several reasons. Majority of the patients (131 or 70.8%) believed that symptoms would pass on their own without seeking care in health care system. Nevertheless, 56 patients (30.3%) reported about postponing care seeking because of lack of health insurance. Communication difficulties with the doctor due to insufficient language skills were not mentioned by any of the patients.

Table 18. Reasons to postpone seeking for medical care among newly detected symptomatic patients with pulmonary tuberculosis, Southern Estonia, 2002–2003

Reason	No (%)
Believing that symptoms would pass on their own	131 (70.8)
Lack of health insurance	56 (30.3)
Concern about spending a long period in hospital	40 (21.6)
Being afraid of the doctor's visit being expensive	38 (20.5)
Lack of a regular or family doctor	28 (15.1)
Fear of what would be found on diagnosis	18 (9.7)
Fear of loss of job or income due to TB	13 (7.0)
Being too busy to seek care	11 (5.9)
Having no idea where to ask for help	8 (4.3)

5.2.8. Patients' Knowledge about Tuberculosis and Reaction to the Diagnosis

Examination of patients' knowledge about TB demonstrated that 174 patients (94.1%) and 157 patients (84.9%) were aware of that TB is an infectious disease and that the main sources of infection are the untreated TB patients, respectively.

Eighty-five patients (46.0%) believed that TB is a curable disease and 35 patients (18.9%) supposed that medicines and treatment in case of TB are free of charge. Simultaneously, 20 patients (10.8%) believed that visits to the family doctor or to the pulmonary physician are not free of charge.

Ninety-eight patients (53.0%) described their reaction to the diagnosis of TB as a shock, fright or fear, 33 patients (17.8%) were unconcerned by their diagnosis and 42 (22.7%) were satisfied, because the reason of their symptoms became evident. Homeless persons (10 or 5.4%). were pleased by the possibility of being admitted to the hospital. Two patients were not able to explain their reaction.

6. DISCUSSION

6.1. Epidemiology of Pulmonary and Extrapulmonary Tuberculosis 1991–2000 (I, II)

Caring for TB patients is one of the unique occasions when clinical practice touches on economics, politics and social sciences, as well as the widest range of medical sciences [27]. This study, designed to analyse the epidemiological situation of TB in Estonia and evaluate the process of diagnosis of TB after overwhelming societal changes and completely modified health care system, highlights important findings for Estonia that can be attributable to several post-socialist countries with similar historical traits.

6.1.1. Incidence Rates

It is impossible to provide one single reason why TB returned as a problem in Estonia after 1992. The incidence rate of new cases of TB in Estonia increased from 21.5/100 000 in 1991 to 44.6/100 000 in 2000 and the simultaneous increase in incidence of TB among children reflected the spread of the infection in the society.

Since TB incidence has increased in all Eastern European Countries after the regaining their independence, the basis for increasing the incidence of pulmonary TB in Estonia could be the recent political and socio-economic changes in the community, which led to outbreaks of communicable diseases like TB. Importantly, the simultaneous changes in the principles of health care management, as well in funding of medical care resulted in instability in health care, including system for TB control [43]. Regardless of almost doubling the amount of incident cases of pulmonary TB from 1991 to 2000, the total number of EPTB remained quite constant. Even over the last 20 years, the number of reported cases of EPTB in Estonia has remained relatively steady at approximately 60 new cases per year. This is in line with an earlier statement by [108], according to which there is no reason to consider that the incidence of EPTB is increasing generally, even in the infected population. This, however, does not explain the differences in the epidemiology of TB of different sites.

As a consequence of the increase in pulmonary TB in Estonia, the proportion of EPTB decreased between 1991 and 2000. The decrease was statistically significant, although adjustment of incidence rates for age in both pulmonary TB and EPTB was not performed. This evidence is in concordance with an earlier opinion, according to which a high incidence of TB in a society is accompanied by a lower percentage of EPTB and a very low incidence of

overall TB, in contrast, is usually accompanied by a relatively higher proportion of EPTB [108].

The absence of both HIV infection and significant immigration probably may stand behind the constancy of the incidence of EPTB in Estonia. The trends that minorities and foreign born people constitute a larger proportion of EPTB than pulmonary cases were also shown in the United States [173], as well as in Western Europe [174, 175]. Immigrants did not play a major role in the epidemiology of overall TB in Estonia: only 13.7% of EPTB and 21.8% of all TB patients were born outside Estonia and no HIV infection was diagnosed among EPTB patients. Nevertheless, the issue of underdiagnosis of EPTB should be discussed, taking into consideration that diagnosis of EPTB is complicated and many studies have pointed out that EPTB is too often diagnosed in an advanced stage [176]. The diagnosis of EPTB can be elusive, necessitating a high index of suspicion [177].

6.1.2. Distribution of Sites of Tuberculosis

Pulmonary TB. The lung remains the main site of clinical TB as it remains the main portal of entry for primary TB infection. The grounds for the decrease in the proportion of so-called less extensive forms of pulmonary TB, which is discovered predominantly by routine medical examination with performing chest X-ray) from 11.8% in 1991 to 2.4% in 2000 could be alterations in prophylactic health care activities. On the other hand, stable proportions of cavitary forms and bacteriologically confirmed diagnoses could be interpreted as a proof of stability of the diagnosing process and its firm quality level.

Extrapulmonary TB. Pleural, bone and joint and lymph node TB were the three leading sites of EPTB in Estonia. Miliary TB, accounting 2.9–18.1% of all cases of EPTB in previous studies [24, 178], was not diagnosed during 1991–2000 in Estonia. One can suppose that Estonian pulmonary specialists have kept to the old practice of entering miliary TB in the record by the clinically most prominent site of the lesion.

When comparing the prevalence of sites of EPTB diagnosed between 1991 and 2000 in Estonia with similar statistics in the USA in the pre-AIDS era (1969–1973), it is noticeable that there are no major differences. However, the proportion of cases of pleural TB is the only exception here: in Estonia, pleural TB accounted for 33.8% of EPTB cases compared to only 26.5% (even 23.7% among White people) in the USA [88, 108]. The data on TB of the lymph nodes is also not always consistent. This site accounted for 20.0% of EPTB cases in Estonia, and 21.3% and 36.5% in the USA and Turkey, respectively [179]. However,

Fain with co-authors (178) has even described lymph node TB in 48.9% of EPTB patients not infected by HIV. Of EPTB sites, the proportion of lymph

node TB has been higher in studies, where the proportion of immigrants from Asia was higher [24, 99, 180, 181].

During the 10-year period, in contrast to the other sites of EPTB, there was a significant increase in so-called early forms of TB. The latter, represented by pleural TB and intrathoracic lymph node TB, occur most frequently with primary infection [181]. This could be explained by a spread of TB infection in the society, because different clinical forms of EPTB develop at different intervals after infection [182, 183]. For instance, tuberculous meningitis tends to be a very early complication, while genitourinary TB usually requires a few decades to manifest [109, 184]. According to the present study, unlike the accepted view [105, 174], the increase in pulmonary TB in Estonia was fortunately not accompanied by an increased incidence of tuberculous meningitis.

6.1.3. Distribution of Sites of Extrapulmonary Tuberculosis by Age and Gender

The proportion of EPTB out of all TB cases decreased significantly with increasing age, patients in the 0 to14-year age group had the highest proportion of EPTB (66.0%), while only 12.1% applies to the entire population. This is not surprising because the proportion of EPTB in children is higher than that in adults in many of the previous studies, albeit still being lower than in our study [100, 185, 186]. We found large differences in distribution according to age for sites of EPTB. Isolated intrathoracic lymph node TB was the most common site of EPTB in children (82% of all cases of EPTB) and there were only two occasions when this disorder was diagnosed in adults. Unlike the trend for isolated intrathoracic lymph node TB [187] in the present study, the proportion of both urogenital TB and osteoarticular TB increased significantly with increasing age. There was only one case of urogenital TB among children and two cases among adolescents during the 10 years. Genitourinary TB is believed to develop most often as the result of recrudescence of long-standing latent tuberculous foci and commonly presents after a long latency period [188]. The vast majority of patients with pleural TB were within the age range of 15–44 years, i.e., they were young adults. Similar results were reported in USA in 1986 [100].

In the present study, other sites of EPTB, like TB of skin, eye and central nervous system were rare and were diagnosed only in adults. This data was in contrast to that obtained in previous studies, which suggest that patients under 15 years of age are most likely to have meningeal TB [23, 189].

There are conflicting opinions about efficacy of he current vaccine, BCG, in preventing infectious TB in countries with a high disease burden [190]. We accept that bacille Calmette-Guérin (BCG)-vaccinations have had a protective

effect against TB forms [191] such as meningeal TB in children in Estonia, since approximately 99% of children were vaccinated with BCG during the first year of life, with a revaccination in 36 to 61% of children at the age of 7 to 8 years [187] and no case of meningeal TB have occurred in children during the last two decades. No differences in BCG-vaccination policies between the Estonian population and immigrants have existed in Estonia. Since 2006, the BCG revaccinations have terminated in Estonia.

The distribution of EPTB cases by gender in the present study significantly differed from that in pulmonary TB (male-female ratios 1.16:1 and 2.62:1, respectively). There is a consistent relative propensity for women with TB to manifest their infections in an extrapulmonary site, which has been addressed earlier, but causes of this phenomenon are unknown [88, 154].

Both in males and females, pleurisy, osteoarticular, genitourinary and lymphatic TB accounted for more than 90% of EPTB. Superficial lymph node TB, but not intrathoracic lymph node involvement had a strong female predominance. The predominance of lymphatic TB among female patients has also been noted in large, detailed reviews [97, 100, 105, 192, 193]. Various male-to-female ratios ranging from 1:1 to 3:1 have been reported in genitourinary TB in different studies [194].

6.1.4. Bacteriological and Histpathological Confirmation of the Diagnosis

Although, the proportion of bacteriologically confirmed cases in EPTB was significantly lower than that in pulmonary TB (40.0% and 71.8%, respectively in 2000), for comparison, in all Europe it was was even lower (26%) [8]. Importantly, in some studies in the USA, the proportion of bacteriologically confirmed cases of EPTB was as high as 69–77% even 1–2 decades ago [100, 108, 195]. The confirmation rate of TB pleurisy in Estonia even decreased during 1996–2000, despite the fact that more efficient diagnostic methods, such as video-assisted thoracoscopic surgery (VATS) were introduced in Estonia during the same period. The laboratory service in Estonia has been supervised by European reference laboratories and is estimated to be at an optimal level. Difficulties associated with specimen sampling or handling may be responsible in some circumstances. The diagnosis and treatment of TB, both pulmonary and extrapulmonary, are subjected to similar principles, the doctors of other specialities widely consult with chest physicians in case of suspicion of TB. However, the management of EPTB often needs tighter collaboration between the chest physician and different specialties in order to settle the issues directly related to the extrapulmonary target organ. A possibility exists that the large proportion of bacteriologically unconfirmed cases of EPTB result in clinical

misdiagnosis of EPTB, which may include both overdiagnosis as well as underdiagnosis.

One can suggest, supporting by earlier data [17] that the overall high prevalence of resistance to anti-TB drugs obviously has a major impact on the current epidemiological situation of TB in Estonia. The current results indicate that the proportion of MDR-TB among EPTB cases was insignificantly lower than in pulmonary TB. The reasons behind that are unclear, but the large proportion of bacteriologically unproven EPTB cases on small numbers of overall EPTB cases most probably play a role. Although maybe not as important issue in EPTB as in pulmonary TB, higher confirmation rate of TB assures proper treatment and limits the spread of TB infection in the society.

6.2. The Process of Diagnosis of Tuberculosis

6.2.1. Patient Characteristics (III, IV)

The strengths of the current study include firstly the fact that unlike in many previous series [4, 23, 26, 32, 34, 196–198], we were able to include all but two patients, who met the study criteria and the problem of insufficient information from doctors to the Estonian Tuberculosis Registry was not the case. Secondly, all interviews in this study were performed not later than one month after the diagnosis, ensuring that the patients remembered well the course of the disease and the diagnosis.

Despite 26.5% of patients were ethnically non-Estonians, all patients had lived in Estonia for more than 10 years and were mostly from Russia. The absence of recent or foreign immigrants among the patients enrolled into the study is characteristic of Southern part of Estonia. This facilitates the study population to conform the requirements in this study.

6.2.2. Patient Delay and Risk Factors for Patient Delay (III)

Both the median and the 75th percentile of the patient delay in Estonia (79 and 140 days, respectively), markedly exceeded that what has been reported in numerous former studies that have assessed similar TB symptoms, but are performed not only in developing countries [6, 33, 38, 121] but also in countries with high income [4, 11, 25] including the 25-day and 32-day median patient delays in New York City [39] and in Maryland [26], respectively. Moreover, the patient delay in Estonia is unreasonably long for a country, where every person should have a personalized family doctor (one per 1900 inhabitants), where all medical services for patients with suspicion of TB are free and independent on

the presence of health insurance and/or place of residence and where all TB drugs are freely received by the patients. Unfortunately, 14.2% of new cases of pulmonary TB in Estonia had MDR-TB in 2004, which makes the situation more alarming.

In general, changes in health care funding could affect accessibility of care, especially replacement of the state funding by health insurance system, which does not automatically cover the whole population. However, this seems not to be the case in Estonian patients, since we detected "living in a rural area" to be the only significant risk factor for prolonged patient delay that could rationally be regarded as a real "barrier" to obtaining care. Male gender and rural residence were the factors significantly associated with prolonged patient delay. High cost-sensitivity of the patients may play a role since, although all medical services were available for all patients on the same level, longer distances between place of living and health care facilities probably required more expenses, as well as more endeavour from the patients. Indeed, the TB patients in the study area not surprisingly belonged to the social group with lower living standard. In this context, travel distances and related transportation costs may create a significant burden on patients [199]. Monthly income less than 333 EUR reported for 95.6% of the patients in the present study was little compared to the mean salary in Estonia (409 EUR per month in 2002).

Unlike in other studies [4, 40, 200], women in Estonia had a significantly shorter prolonged and extreme patient delay. Provided that all levels of health care are equally accessible for males and females and no prejudice exists in this subject, it may be possible that females tend to be more concerned about themselves' health and are consequently more active to seek for help due to their symptoms.

Unexpectedly in the light of many previous reports, patient delay in the present study was not associated with such potential risk factors like foreign ethnicity, unemployment [38, 119] and age [40], suggesting that the patients in the study area were not facing inequitable barriers to care. In Estonia, unemployment automatically accompanies with the lack of health insurance and hence, difficulties in getting medical care. Simultaneously, unemployment could be linked with more difficult economic situation. However, the latter link is not as frank as widely believed. Taking this into consideration, in the present study, unemployment was designed to serve as a joint variable to express the risks of missing health insurance and difficult economy. In the present study, unemployed people, although left without health insurance, did not experience a greater hesitation in turning to the doctor than did other members of the society.

The influence of immigration has most likely been insignificant in Estonia, because until the declaration of independence in 1991, Estonian frontiers were closed. Despite about one sixth of the patients in the study area were foreign-born, the whole population was nevertheless quite homogeneous on the cultural and behavioural point of view because all patients had lived in Estonia for more

than 10 years. To our opinion, this fact explains why patients' nationality was not correlated with either prolonged or extreme patient delay in our study and why there were no registered complaints about language difficulties.

Based on previous studies from regions with different cultural background, patients' education level is one of the important factors, influencing the duration of the patient delay [6, 118, 196]. Illiterate people and patients with lower education have been found to be more prone to prolonged patient delay. Due to a more fortunate situation of education in Estonia where illiterate persons do not exist at all, we had to compare the patient delay among patients with primary, basic and occupational education with the patients with secondary, vocational and university education. Surprisingly, neither of the two education-based patient subpopulations had a statistically significant association with the patient delay. One could thus conclude that although the higher education improves the mental outlook, it does not necessarily guarantee a better realization of the significance of symptoms, which usually would refer to TB.

6.2.3. Health System Delay and Risk Factors for Health System Delay (IV)

This study highlights two important findings for Estonia that can be attributable to several post-socialist countries with similar historical traits. First, substantial social, economic and political changes involving modifications in health care system after 1991 could be performed without significantly increasing HSDs in diagnostic evaluation of patients with pulmonary TB. Secondly, with regard to the HSD, it makes no difference, whether the first doctor, whom the patient contacts, is a family doctor, pulmonary physician or other specialist.

Ten years after the reformation of the health care system, the median of HSD in Estonia was 19 days, which is similar to that reported in previous studies from other countries, independently on societal evolution and income level: 14 days in Tanzania [41] and 19.6 days in Japan [127]. Because of the lack of data about HSD before the health care reformation in Estonia, we cannot analyse, whether HSD had changed significantly. However, based on comparisons with data from other countries, the duration of HSD found for Southern Estonia is optimal. Several factors may account for this result. First, the great majority of Estonian patients are younger and in working age, which makes the diagnosis of TB less complicated. Our present finding of older age being a risk factor for HSD supports this opinion. Furthermore, prolonged HSD has been linked to an advanced age also in other countries, [11, 123] as it is associated with higher rates of co-morbidities in the elderly. This could also be the case in Estonia. Indeed, symptoms of pre-existing chronic illnesses can be misinterpreted as symptoms of TB when reporting about the symptoms onset [11]. On the other hand, masking of TB symptoms by signs of exacerbation of chronic cardio-

respiratory diseases in the elderly is possible as well. Even changed characteristics of the clinical course of TB in the elderly impeding the diagnosis cannot be excluded in this context. Secondly, free access to the medical care supports the issue of patients' collaboration with health care services.

Some additional factors could have facilitated the process of diagnosing TB. One of the factors positively influencing the quality of diagnosing TB could be maintenance of considerable proportion for TB in the academic curriculum for both graduate and post-graduate students and junior doctors in the Medical Faculty. In reality, the courses of TB in Estonia are carried out by professors, who also practice as pulmonologists and whose personal practical experiences could be passed to young doctors. Although the finding of the present study that the period of HSD was independent on the specialty of the first doctor, whom the patient contacted, is in conflict with earlier studies [11], it could be explained by a good awareness about TB in general practice. Straight after the implementation of the Estonian National TB Program in 1997, its subprograms of regular education were launched in order to educate doctors of all specialities, especially family doctors, to recognize and diagnose TB. On the other hand, one can suppose that Estonian doctors of almost all specialities have kept to the old successful practice of sending patients with suspicion of TB to the chest physician as quickly as possible because of the probability of infectiousness. In 55.7% of cases in our study, medical assistance was first sought from a general practitioner. This proportion should be increased and the proportion of cases, when the patients first turned to an emergency department or TB was discovered by doctors of other specialties (26.5%), must decrease. Patients in Estonia used to turn for the emergence aid in case of high fever or severe cough, but these cases usually represent advanced stage of TB. None of the patients sought care at the private sector, probably because of the awareness of this action being not free of charge. On the opposite, healthcare seeking from the family doctor is more popular because of similarities with the district-doctor system in the Soviet Union.

Non-native and unemployed people had a shorter HSD in our study, as in several previous studies [122, 132, 201]. In Estonia, all residents have equally free access to public medical care, including family doctors and pulmonary physicians, for TB and emergencies, independently on their employment status and nationality. As status of unemployment did not represent a risk factor for HSD, we additionally analysed absence of health insurance as risk factor for prolonged health system delay. It revealed that people without health insurance had a shorter HSD as well (Tables 15 and 16). Because a real immigration still did not exist in Estonia during the study, it is difficult to explain why shorter HSD was present in non-Estonians. Since according to an earlier study showing that current non-native nationality is a risk factor for being ill with TB in Estonia [64] the hypothesis of higher suspicion for TB in non-Estonian patients among the medical practitioners could be arisen. Although the current study did

not address this issue, we can only speculate that non-Estonian patients tend to present with more advanced disease or they collaborate more actively with health care services in diagnosing TB.

Smear microscopy, sputum culture and chest X-ray have been made in all cases of pulmonary TB in our study, but doctors in Estonia quite often start only with X-ray as a rule. The fact that non- or under-utilisation of smear microscopy, sputum culture or chest X-ray in the diagnosis of TB influences the period of HSD has been confirmed by earlier studies [25, 116]. Unfortunately, in 47.6% of cases in our study, the doctors had not taken the possibility of TB into consideration and even X-ray was not performed during the first visit. On the other hand, we did not find an association between a history of TB contacts and either prolonged or extreme HSD. Earlier studies [25] have demonstrated a shorter HSD if the doctor had enquired about a history of TB in the family. Referring to the medical records as source data and having interviewed the patients *post hoc*, we can only consider that the doctors did not ask patients about the history of their TB contacts. Hence, we believe that respective questioning of patients could have been lead to X-ray studies in time.

The proportions of smear-negative TB and cases without cough were quite substantial, accounting for 44.9% and 27.6%, respectively in this study. Smear negativity and absence of cough as risk factors for prolonged and extreme HSD could be associated with atypical course or less extensive forms of TB. According to the present knowledge, the diagnosis of smear negative TB requires a minimum of two weeks and extends the period of doctor delay [6]. Instead, smear-positive cases could be diagnosed more quickly, but the need for new diagnostic methods still exists to elucidate drug sensitivity of *Mycobacterium tuberculosis*.

6.2.4. Patient Delay, Health System Delay and Total delay (III, IV)

The median HSD in our study was only one quarter of the median of the patient's delay (19 versus 79 days). Similar results, where patient delay was the major contributor to the overall or total delay, have been reported in previous studies from Ethiopia [6], Nigeria [38] and east London [128]. Socio-economic and societal barriers in getting health care stand behind the long patient delay.

The situation, when HSD exceeds patient delay, has been reported in Australia [120], Malaysia [112], Botswana [36], Ghana [33], Turkey [200], Japan [202] and Thailand [145], and was explained by the lack of diagnostic awareness among health care workers and atypical presentation of TB [142–144]. Nevertheless, patient delay and HSD were negatively correlated to each other in the majority of previous studies [25, 36, 124] with only few exceptions [32, 127]. The long patient delay may make the diagnosis of TB easier as patients present at a more advanced stage and hence, with more characteristic clinical picture.

6.2.5. Symptoms of Tuberculosis (III)

The vast majority of the patients with pulmonary TB in Southern Estonia (95.4%) declared the presence of at least one symptom. Out of 194 cases otherwise eligible for the study, only nine patients (4.6%) were without symptoms and were excluded according to the protocol. This is in line with the presentation of pulmonary TB in general, Mori with co-authors [114] have found this proportion being even 98.7%. The mean number of TB symptoms reported by the patients during their illness in our study (5.5) concords with the data from Thailand, where 5.9 symptoms per patient were registered [37].

The three leading symptoms in our study patients, cough, fatigue and fever, should warrant more attention by both health care workers and patients, because they predominated among the all symptoms and among the first symptoms as well. Appearance of the commonest symptoms as cough, fever, sweats, anorexia, chest pain and weight loss were similar among the TB patients in the present study and New York [39] despite the fact that the ethnic and racial composition of the study population in New York was heterogeneous and thus quite different from that in the present study, with the only exception of fatigue that showed higher prevalence in Estonia. Similar results have also been demonstrated in Ghana [33]. Some authors have found that the presence of productive cough among the symptoms, even when associated with haemoptysis, did not lead to shorter delays [119], or was even risk factor for prolonged patients delay [25]. Our aim was to unravel the impact of each particular TB symptom on making the patient's decision to seek medical care. We therefore compared the medians of patient delay by the firstly noticed symptom assuming that the more serious first symptom on the patient's point of view, the shorter is the patient delay. In the light of this postulation, our analysis revealed that the patients tend to pay most attention to fever and chest pain, but, surprisingly, when the first symptoms were cough or loss of appetite, the lengths of the delay were maximal.

As a half of the patients turned to the doctor after having coughed for more than 3 months, it is not fully clear, why cough, generally known as a major disturbing symptom and a well-known cause of seeking care [203] does not impel the patient to turn to the health care provider for help when TB is the case. A population-based survey in Vietnam supports our results by showing that many of those, who had coughed for more than 3 weeks, had had symptoms for more than 3 months [204]. One could speculate that cough is, like loss of appetite, a very prevalent and highly non-specific [205] symptom among the people, thus maybe too common thing rather than a sign of a serious illness to urge medical consultation.

More surprisingly, although haemoptysis is closely connected with coughing, among those four patients, who declared haemoptysis as the first symptom in our study, the median of the patient delay was the longest. This

evidence, though based only on four patients, is in conflict with that reported in previous studies [35]. The analysis of these four cases revealed that the patients probably were not able to realise their symptoms because of underlying disease: severe chronic obstructive lung disease (2 cases), lung carcinoma (1 case) and alcoholic brain atrophy (1 case). There are also data on that haemoptysis may not be a serious symptom in patients' point of view. Lienhardt and co-authors [7] have reported no difference for patient delay between patients, who had blood in sputum during their symptomatic period and those without haemoptysis. The significance of haemoptysis for the patient may, however, depend on the timing of the occurrence of this symptom. For example, in subjects, who described having blood in their sputum at onset of symptoms, the median delay was significantly shorter [7]. In general, one should suspect TB in every person with cough lasting for 3 weeks.

The interpretation and evaluation of their symptoms made difficulties for the patients indeed, because only as few as 14.6% of patients in our study suspected TB as the cause of their symptoms. Although, this percentage was 57% in Los Angeles [34] and in Malawi [206]. Liam has demonstrated an absence of shorter patient delays even in patients who were able to associate their symptoms with TB [112].

In addition, TB symptoms can also often be misinterpreted as symptoms of a common cold, as did 53.5% of patients in the present study and 53.8% of patients in Japan [124]. Our data support public-educational efforts to encourage persons with TB, who are unaware of the grave significance of their symptoms, to seek care when durable symptoms, especially cough lasting over 3 weeks, are present.

6.2.6. Remedial Actions Undertaken by the Patients due to their Symptoms (III)

Analyzing patients' behaviour during the period from the first symptom to the first contact with the health care provider, we found that surprisingly, the guiding principle of the greatest proportion of the TB patients during the period of experiencing symptoms was waiting, followed by having more rest, or ingesting medicines available without a medical prescription, mainly those, which reduce fever or cough. This finding is very similar to the data from Ethiopia [6], New Zealand [25] and Kuala Lumpur [112], the countries with rather different cultural and socio-economical background, stressing the possibility that patients' behaviour is almost independent on the background of their country of living. The belief in the efficacy of self-treatment has been reported as a risk factor for patient delay and could have influenced the length of patient delay in our study as well. Remarkably, increased alcohol intake was more popular than reduced alcohol intake among the patients in our study.

6.2.7. Reasons to Postpone Seeking for Medical Care by the Patients (III)

The great majority of the patients postponed the health seeking because of their belief in that symptoms would pass on their own (70.8%). It is not easy to interpret this attitude, but it has been found to be the risk factor for prolonged patient delay [25]. Fear of what would be found as diagnosis was not among the main reasons for postponing health care seeking in the present study (9.7%), but generally, it is regarded as a risk factor for patient delay as well [25]. Lack of health insurance and being afraid of the doctor's visit being expensive were highlighted as reasons to postpone seeking of medical care by 30.3% and 20.5% of the patients, respectively. These causes could make reference to the sources of the reasons, why both the median and the 75th percentile of the patient delay in Estonia markedly exceeded those reported in numerous former studies.

6.2.8. Patients' Knowledge about Tuberculosis and Reaction to the Diagnosis

Differently from a study from Tanzania [207] knowledge about essence of TB is generally high in Southern Estonia, but increasing awareness of the population of freely accessible health care resources in case of TB is always warranted.

The majority of patients (53.0%), after becoming aware of their diagnosis of TB, experienced a shock, fright or fear. This reaction could be based on the historical memory of the Estonian society according to which TB used to be evaluated as a serious, sometimes fatal disease with severe complications long-lasting consequences. Accordingly to earlier studies, the main factors contributing to the delay in health seeking are fear of social isolation in the family and in the community and economic constraints [208]. TB patients are almost universally unaccepted by the communities in different countries independently on the cultural background and the increased social stigma with isolation of TB patients and their families has a tendency to continue much further than that is medically reasonable [147, 148, 209]. Probably due to the same reasons, the proportion of patients, who reported themselves as being satisfied because the reason of their symptoms became evident, was comparatively low (22.7%). Homeless persons, who felt themselves lucky because of the possibility to be admitted to the hospital (5.4%), could be also added into this group of satisfied patients.

7. CONCLUSIONS

1. The incidence of EPTB in Estonia between 1991 and 2000 increased significantly less than did pulmonary TB resulting in a decrease in the proportion of EPTB among the overall TB.
2. The number of cases of EPTB forms with a short latent period (e.g. intrathoracic lymph node TB and tuberculous pleurisy) increased along with pulmonary TB reflecting the high spread of TB infection in the community during the 10 years.
3. The proportion of less extensive forms of pulmonary TB decreased from 1991 to 2000, suggesting a considerable delay in the diagnosis.
4. The highest proportion of EPTB of the total TB was in children, resulting in that the proportion of EPTB out of all TB decreased significantly with increasing age. Distinct sites of EPTB were associated with certain age: isolated intrathoracic lymph node TB was the most common site of EPTB in children, most of pleural TB occurred within the age range of 15–44 years, i.e. in young adults, whereas the proportion of both urogenital and osteoarticular TB significantly increased with increasing age.
5. Pleurisy, osteoarticular, genitourinary and lymphatic TB accounted for more than 90% of EPTB without significant gender preponderance. Superficial lymph node TB, but not intrathoracic lymph node involvement, had a strong female predominance.
6. The proportion of bacteriologically and/or histopathologically confirmed cases of EPTB was significantly lower than that of pulmonary TB. The confirmation rates differed also among the different sites of EPTB being higher in urogenital and pleural TB and lower in intrathoracic lymph node and osteoarticular TB.
7. The length of the patient delay in Southern Estonia exceeded that found in former studies, thus the duration of HSD may be considered optimal.
8. Family doctors could successfully manage with diagnosing pulmonary TB as there were no differences for patient delay between the medical specialties the patients contacted first.
9. Male gender and rural residence were the risk factors for both prolonged and extreme patient delay, whereas foreign ethnicity and unemployment were not.
10. Smear negativity and absence of cough among the symptoms, referring to an atypical course or less extensive forms of pulmonary TB, missed X-ray during the first visit, and patient's age over 60 years were the risk factors for prolonged and extreme HSD. Unemployment, missing health insurance and non-native nationality, the features generally associated with less coverage by medical attention, resulted in even shorter HSD.
11. The vast majority of patients with pulmonary TB were symptomatic. Cough, fatigue and fever predominated both among the all symptoms and

among the firstly developed symptoms. The patients paid most attention to fever and chest pain. Cough, even with haemoptysis, did not represent a serious symptom on the patients' point of view.

12. Being ill with TB was a minor suspect among the symptomatic TB patients. Waiting or ingesting medicines available without a medical prescription was the guiding principle of the majority of TB patients during their symptomatic period. The main reasons of postponing the health seeking (hope that symptoms would pass on their own, fear of the diagnosis of TB, lack of health insurance and being afraid of the doctor's visit being expensive) refer to the reasons, why the patient delay in Southern Estonia was unexpectedly long.

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9. SUMMARY IN ESTONIAN

Tuberkuloosi epidemioloogiline olukord Eestis 1991–2003 rõhuasetusega kopsuvälisele tuberkuloosile ja kopsutuberkuloosi diagnoosimise viivitust mõjutavatele teguritele

Ida-Euroopas ja endistes Nõukogude Liidu vabariikides 1990. aastatel toimunud poliitilised, sotsiaalsed ja majanduslikud muutused avaldasid tugevat mõju tervishoiusüsteemile [210–212]. Eestis hakkas tuberkuloosi haigestumus suurenema taasiseseisvumise järel 1991. a., pärast aastakümneid kestnud langustrendi. Tuberkuloosi (TB) esmashaigestumuskordaja tõusis 1992–2000 kahekordseks, olles 1992. a. 26 ja 2000. a 58 (100 000 in. kohta) [2]. Tuberkuloosihaigestumust Eestis ei ole seni mõjutanud HIV infektsiooni suurenenud levik ega immigratsioon. Tuberkuloos (TB) võib haarata kõiki organsüsteeme, kuid vähe on andmeid kopsuvälise ehk ekstrapulmonaalse tuberkuloosi (EPTB, *extrapulmonary tuberculosis*) epidemioloogilise olukorra kohta kopsutuberkuloosi sagenemise tingimustes, kus puudub immigratsiooni ja HIV infektsiooni mõju [24, 176].

Tuberkuloosse infektsiooni leviku tõkestamisel on kõige olulisem TB õigeaegne diagnoosimine ja ravi [25]. On kindlaks tehtud, et ravimata TB-haige võib haigusperioodil nakatada umbes 20 inimest [28, 60]. Seetõttu on oluline, et ajavahemik sümptomite tekkimisest TB diagnoosimiseni oleks võimalikult lühike. Täpsemaks analüüsiks jagatakse nimetatud periood kaheks osaks:

1) patsiendi viivitus, mis kestab esimese sümptomi tekkimisest patsiendi pöördumiseni arsti poole, ja
2) arsti viivitus ehk tervishoiusüsteemi viivitus, mis kestab vastavalt esimesest arstivisiidist diagnoosimiseni. TB kiiremaks avastamiseks ja diagnoosimiseks ning TB infektsiooni leviku piiramiseks on oluline analüüsida patsiendi viivituse ja tervishoiusüsteemi viivituse pikkust ning eeskätt neid mõjutavaid tegureid.

Varasemate uuringute alusel on pikenenud patsiendi viivituse riskiteguriks kõige sagedamini arstiabi halb kättesaadavus: töötu staatus ja haiguskindlustuse puudumine, elukoht maal [7, 33, 114], immigrandi status [40] ja immigrantide keelebarjäärid [39]. Hiljem pöörduvad arsti poole ka naised [121]. Teiste tegurite mõjust patsiendi viivituse pikkusele on tulemused vastukäivad. Patsiendi viivituse pikenemise riskiteguriks võib olla vanus ≥65 aastat [4, 11], vanus ≤65 aastat [131], perekonnaseis abielus [35] või vallaline [37]. Varem läbi viidud uuringute põhjal mõjutavad tervishoiusüsteemi viivituse pikkust haigusprotsessi vorm ja staadium, arstiabi kättesaadavus ja meditsiinipersonali teadmised [7].

Käesoleva ajani ei ole uuritud tervishoiusüsteemi valmisolekut diagnoosida TB pärast suuri poliitilisi muutusi, millega kaasnes üleminek turumajandusele ja ümberkorraldused tervishoiusüsteemis.

Pärast Eesti taasiseseisvumist 1991. a. asendus tervishoiusüsteemi riiklik finantseerimine haigekassasüsteemiga, kuid ravikindlustus ei hõlmanud automaatselt kõiki inimesi. Eestis loodi perearstisüsteem ning võimalused eraarstide tegevuseks.

Tuberkuloosialast tegevust koordineerib alates 1997. a. riiklikult finantseeritav Eesti tuberkuloositõrje programm, mille peamised töövaldkonnad on tuberkuloosiregistri, laboriteenistuse ja otseselt kontrollitava ravisüsteemi töö organiseerimine, tuberkuloosiravimite tarnimise ja meditsiinipersonali koolituse korraldamine [43]. Tuberkuloosidispanserite tööd jätkasid polikliinikute TB-kabinetid. Ümber hinnati TB ravi põhimõtted: kasutatakse standardseid raviskeeme ja otseselt kontrollitavat ravi (DOTS), tunduvalt suurenes ambulatoorse ravi osatähtsus: TB haiglavoodite arv vähenes 875-lt 1991. a 291-le 2000. a. Kõik tuberkuloosisanatooriumid (250 kohta) suleti. TB statistiline aruandlus seati vastavusse Maailma Terviseorganisatsiooni soovitustega, uuenes kopsuvälise TB määratlus. Kopsutuberkuloosi ja kopsuvälise TB diagnoosimise põhimõtetes uuritaval perioodil suuri muutusi ei olnud.

UURINGU EESMÄRGID

Uuringu eesmärk oli analüüsida TB epidemioloogilist olukorda Eestis 1991–2000. a. ja TB diagnoosimise protsessi Eestis pärast poliitilisi ja sotsiaalmajanduslikke muutusi, mis järgnesid taasiseseisvumisele 1991. a. Samuti oli eesmärgiks analüüsida patsiendi viivituse ja tervishoiusüsteemi viivituse pikkust ning neid mõjutavaid tegureid.

Uuritavat perioodi iseloomustas suurenenud haigestumus kopsutuberkuloosi, kuid olulise iseärasusena ei olnud see mõjutatud HIV infektsiooni suurenenud levikust ja immigratsioonist.

1) Analüüsida retrospektiivselt sotsiaalmajanduslike muutuste mõju kopsutuberkuloosi ja kopsuvälise tuberkuloosi epidemioloogiale Eestis aastatel 1991–2000.
2) Analüüsida kopsuvälise TB ja selle paikmete sagedust vanuserühmiti ja soo järgi ning bakterioloogiliselt tõestatud haigusjuhtude esinemist kopsutuberkuloosi haigestumuse kasvu tingimustes.
3) Selgitada patsiendi viivituse ja tervishoiusüsteemi viivituse pikkus ning seda mõjutavad riskitegurid Eestis kopsutuberkuloosi korral.
4) Selgitada kopsutuberkuloosi peamiste sümptomite levimus ja esimesena tekkinud sümptomite levimus Eestis.
5) Analüüsida tuberkuloosisümptomite interpreteerimist patsientide poolt ning patsientide reageerimist sümptomitele ja TB diagnoosile.

UURITAVAD JA MEETODID

Tuberkuloosi epidemioloogiline olukord Eestis 1991–2000

Retrospektiivselt analüüsiti Eestis 10 aasta jooksul (1991.–2000. a.) diagnoositud ja vabariiklikus andmebaasis arvele võetud uusi TB juhte. Teostati ümberarvestused seoses kopsuvälise TB määratluse muutustega 1996. a. Haigustekitaja, *Mycobacterium tuberculosis*'e ravimtundlikkuse kohta on andmed olemas alates 1994. aastast. Analüüsiti haigestumust kopsutuberkuloosi ja kopsuvälisesse TB, selgitati kopsuvälise TB enamdiagnoositud paikmete suhteline sagedus ja selle muutus vaatlusperioodi jooksul ning selgitati kopsuvälise TB jaotust paikmeti ja vanuserühmiti. Analüüsiti kopsutuberkuloosi ja kopsuvälise TB paikmete bakterioloogiliselt kinnitunud diagnooside sagedust.

Kopsutuberkuloosi diagnoosimise protsess Eestis, viivitus diagnoosimisel ja seda mõjutavad tegurid

Uurimistöö viidi läbi Lõuna-Eesti kuues maakonnas (Tartu, Võru, Põlva, Jõgeva, Valga ja Viljandi), mille rahvastik moodustab 26% Eesti rahvastikust. Uuringusse lülitati kõik uued, sümptomitega, bakterioloogiliselt tõestatud diagnoosiga ja Eesti tuberkuloosiregistris 2002.–2003. a. registreeritud kopsutuberkuloosihaiged vanuses ≥16 aastat. Patsiente intervjueeriti 30 päeva jooksul pärast diagnoosimist. Lisaks demograafilistele andmetele koguti andmeid võimalike kontaktide kohta TB-haigetega, sümptomite esinemise ja nende tekkimise aja, arsti poole pöördumise kuupäeva, arsti ning arsti korraldatud uuringute kohta. Uuriti patsiendi põhjendusi, miks arsti poole pöördumisega viivitati, patsiendi seletusi sümptomitele ja patsiendi tegevust sümptomite leevendamiseks enne arsti poole pöördumist. Kliinilised andmed koguti meditsiinilisest dokumentatsioonist.

Meditsiinitöötajad, kelle poole patsiendid pöördusid, jagati kolme gruppi: kopsuarstid, perearstid ja teised. Viimasesse gruppi kuulusid kõikide teiste erialade arstid ja meditsiiniõed.

Patsiendi viivituse ja tervishoiusüsteemi viivituse mõiste

Patsiendi viivitus on ajavahemik päevades esimese sümptomi tekkimisest kuni patsiendi arsti poole pöördumiseni [5, 6].

Pikenenud patsiendi viivitus – olukord, kus patsiendi viivitus on pikem kui median [11].

Äärmuslik patsiendi viivitus – olukord, kus patsiendi viivitus on pikem kui 75. protsentiil [4].

Tervishoiusüsteemi viivitus on ajavahemik päevades patsiendi esimesest pöördumisest arsti poole kuni TB diagnoosimise kuupäevani [6].

Pikenenud tervishoiusüsteemi viivitus – olukord, kus tervishoiusüsteemi viivitus on pikem kui mediaan.

Äärmuslik tervishoiusüsteemi viivitus – olukord, kus tervishoiusüsteemi viivitus on pikem kui 75. protsentiil.

Arvutati patsiendi ja tervishoiusüsteemi viivituse pikkuste mediaanid ja 75. protsentiilid päevades. Arvutati ka patsiendi viivituse pikkuse mediaanid esimesena tekkinud sümptomite kaupa.

Statistilises analüüsis kasutati χ^2 neliktabeltesti ja χ^2 trenditesti. Patsiendi ja tervishoiusüsteemi viivituste seoseid riskiteguritega uuriti, kasutades logistilist regressioonanalüüsi koos šansisuhte ja 95% usalduspiiride arvutamisega.

Kõik uuringuprotokollid on heaks kiitnud Tartu Ülikooli inimuuringute eetika komitee. Kõik patsiendid andsid kirjaliku nõusoleku uuringus osalemiseks. Uuringus osalemisest keeldujaid või patsiente, kes oleksid uuringu katkestanud informeeritud nõusoleku tagasivõtmise teel, ei olnud.

TULEMUSED

Tuberkuloosi epidemioloogiline olukord Eestis 1991–2000

Tuberkuloosi esmashaigestumus oli 1991. a. 21,5 ja 2000. a. 44,6 100 000 inimese kohta. Kopsuvälise TB esmashaigestumus oli nendel aastatel vastavalt 3,6 ja 4,7**.** Tegemist on seega kopsutuberkuloosijuhtude arvu kahekordistumisega (1991. a. 279 ja 2000. a. 577 uut juhtu), kuid samal ajal püsis kopsuvälise TB uute juhtude arv suhteliselt stabiilsena: 60–70 juhtu aastas. Tulenevalt kopsutuberkuloosi haigestumuse suurenemisest vähenes kopsuvälise TB suhteline sagedus 17,0%-lt 1991. a. 10,1%-le 2000. a. Kokku haigestus 1991–2000 tuberkuloosi 5365 inimest, neist 622-l diagnoositi kopsuväline TB. Kümne aasta jooksul oli kopsuvälise TB enimdiagnoositud paikmeks tuberkuloosne pleuriit nii meestel kui naistel, vastavalt 37,1% ja 29,9% kõigist meestel ja naistel diagnoositud kopsuvälise TB juhtudest. Sellele järgnes naistel lümfisõlmede TB (22,5%) ning meestel luu- ja liigesetuberkuloos (21,6%). Sarnaselt varasemate uuringutega [24] esines perifeersete lümfisõlmede TB naistel rohkem kui meestel, vastavalt 12,8% ja 4,8%. Erinevus puudus intratorakaalsete lümfisõlmede osas (meestel 13,5% ja naistel 9,7%), vastavad võrdlusandmed kirjanduses puuduvad. Kopsuvälise TB enamdiagnoositud paikmete suhteline sagedus muutus vaatlusperioodi (1991–2000) jooksul. Statistiliselt suurenes oluliselt intratorakaalsete lümfisõlmede TB haigusjuhtude arv ($p<0.05$), mis on seletatav üldise laste tuberkuloosi haigestumuse kasvuga. Teiste paikmete, kaasa arvatud naha, silma, maksa ja soole TB, juhtude arv vähenes ($p<0.05$); luu- ja liigese TB ja urogenitaaltrakti TB juhtude arv oluliselt ei muutunud.

Kopsuvälise TB sagedus vanuserühmiti oli erinev. Kümne aasta jooksul haigestus tuberkuloosi 126 last (0–14 a.), neist 83-l (66%) diagnoositi kopsuväline TB. Täiskasvanutel moodustas kopsuväline TB ainult 10% (514 juhtu). Noorukid (15–17 a.) jäid oma näitajatega laste ja täiskasvanute vahele, kopsuväline TB moodustas neil 35%.

Kopsuvälise TB paige sõltub samuti vanusest. Lastel esines kõige enam intratorakaalsete lümfisõlmede TB (80,7%), täiskasvanutel oli esikohal tuberkuloosne pleuriit (38,3%), järgnesid luu- ja liigese- (23,0%) ning urogenitaaltrakti TB (21,4%).

Kümne aasta jooksul esines noorukitel kopsuvälist TB 25 juhul, neist 40% oli tuberkuloosset pleuriiti ja 16% intratorakaalsete lümfisõlmede, perifeersete lümfisõlmede ning luu- ja liigesetuberkuloosi. Vanuse kasvuga intratorakaalsete lümfisõlmede TB sagedus vähenes, ($p<0.05$), luu- ja liigese- ning urogenitaaltrakti TB sagedus aga suurenes ($p<0.05$). Vähemlevinud kopsuvälise TB paikmeid (kesknärvisüsteemi, naha ja silma TB) esines ainult täiskasvanutel.

Kopsuvälise TB diagnoosi bakterioloogilist/histoloogilist kinnitust analüüsiti 1996.–2000. a. diagnoositud haigusjuhtudel. Uuringu andmetel on kopsuvälise TB paikmete korral bakterioloogiliselt või histoloogiliselt kinnitunud diagnooside sagedus erinev. Nii leidis urogenitaaltrakti TB kinnituse 71,4% 1996. a., 26,7% 1997. a., 85,7% 1998. a., 66,6% 1999. a. ja 50% 2000. a. Üllatuslikult vähenes mikrobioloogiliselt/histoloogiliselt kinnitunud tuberkuloosse pleuriidi sagedus 70,6%-lt 1996. a 56,3%-le 2000. a. Luu- ja liigesetuberkuloosi juhtudest oli 21,4% 1999. a. ja 20% 2000. a. kinnitunud bakterioloogiliste või morfoloogiliste uuringutega. Mikrobioloogilise või patoloogilise diagnoosini on sagedamini jõutud tuberkuloossete spondüliitide korral, kus haiguse kulg on tinginud neurokirurgilise sekkumise. Bakterioloogiliselt kinnitunud kopsuvälise TB juhtude hulgas diagnoositi 6 multiresistentse tuberkuloosi (*multidrugresistant tuberculosis*, MDR-TB) juhtu: 3 juhtu (9,7%) 1998. a., 2 juhtu (8%) 1999. a. ja 1 juht (3,8%) 2000. a. Kopsutuberkuloosi korral oli MDR-TB sagedus suurem (11,1% 1997. a., 14,1% 1998. a., 17,1% 1999. a. ja 12,0% 2000. a.), kuid statistilist erinevust kopsuvälise TB-ga ei olnud ($p>0.05$).

Kopsutuberkuloosi lagunemistega vormid moodustasid 1991. a. 65,6% ja 2000. a. 82,1%. kõigist kopsutuberkuloosi juhtudest. Kuid kopsutuberkuloosi väikevormide (lesioon <1cm) sagedus diagnoosimisel vähenes 33-lt (11,8%) 1991. a. 14-le (2,4%) 2000. a., mis viitab võimalikule hilinemisele TB diagnoosimisel.

Kopsutuberkuloosi diagnoosimise viivitused ja neid mõjutavad tegurid

Lõuna-Eesti kuues maakonnas 2002.–2003. a. diagnoositud kopsutuberkuloosi patsientidest sobis uuringusse 187, kuid 2 haiget kadus meditsiinisüsteemist pärast diagnoosimist. Seega lülitati uuringusse 185 patsienti. Kuigi 16,8% uuritavatest olid sündinud väljaspool Eestit ja 26,5% olid mitte-eestlased, olid

kõik patsiendid elanud Eestis rohkem kui 10 aastat ja ainult 3 neist (1,6%) olid elanud Eestis vähem kui 20 aastat. Kõik 175 patsienti (94,6%), kes olid testitud HIV suhtes, olid HIV-negatiivsed, 7 patsienti (3,8%) oli uurimata, ühel juhul (1,6%) aga testi tulemus teadmata.

Tuberkuloosi sümptomid

Väsimus esines 148-l (80,0%), köha 133-l (71,9%) ja palavik 128-l (69,2%) patsiendil. Sagedamini kirjeldatud sümptomid olid veel rögaeritus (89 patsienti, 48,1%), kaalulangus (86 patsienti, 46,5%) ja higistamine (79 haiget, 42,7%). Köha, väsimus ja palavik olid ka kõige sagedasemad esimesena tekkinud sümptomid. Keskmiselt esines uuritaval 5,5 sümptomit. Üle poolte uuritavatest, 101 (54,6%), arvas sümptomite põhjuseks olevat külmetuse, 14 (7,6%) üleväsimuse ja 7 (3,8%) kroonilise kopsuhaiguse ägenemise. Ainult 27 uuritavat (14,6%) kahtlustas TB-d.

Pöördumine arsti poole

Sümptomite tõttu pöördus aktiivselt arsti poole 161 uuritavat (87,0%), ülejäänud, kuigi sümptomitega, pöördusid kas kohustuslikuks regulaarseks profülaktiliseks läbivaatuseks (17 uuritavat, 9,2%) või kontrolliks tuberkuloosihaige kontaktsena (7 uuritavat, 3,8%). Üle poole uuritavatest, 103 (55,7%), pöördus esimesena perearsti poole ning 28 uuritavat (15,1%) kopsuarsti poole. 49 juhul (26,5%) kontakteerus uuritav esimesena teiste erialade arstidega, k.a. erakorralise meditsiini arstid, viiel juhul meditsiiniõega. Pöördumisi eraarstide poole ei registreeritud.

Patsiendi viivitus ja selle pikenemise riskitegurid

Patsiendi viivituse mediaan ja 75. protsentiil olid vastavalt 79 ja 140 päeva. *Pikenenud patsiendi viivituse* riskitegurid olid meessugu ja elukoht maapiirkonnas. *Äärmusliku patsiendi viivituse* riskitegur oli ainult elamine maal.

Pikenenud ega äärmuslikult pikenenud patsiendi viivitusel ei leitud seost uuritavate vanuse, rahvuse, perekonnaseisu, haridustaseme, töökoha ega haiguskindlustuse olemasolu või puudumisega.

Patsiendi viivituse pikkust analüüsiti ka seoses esimesena tekkinud sümptomiga.

Patsiendi viivituse mediaan oli lühem, kui esimene sümptomina tekkis palavik (mediaan 22 päeva) või valud rindkeres (mediaan 33 päeva), ning pikem, kui esimesed sümptomid olid vereköha (mediaan 196 päeva), köha (mediaan 99 päeva) või isutus (mediaan 98 päeva).

Tervishoiusüsteemi viivitus ja selle pikenemise riskitegurid

Tervishoiusüsteemi viivituse mediaan ja 75. protsentiil olid vastavalt 19 ja 40 päeva. *Pikenenud tervishoiusüsteemi viivituse* riskitegurid olid köha puudumine, bakterierituse puudumine röga äigepreparaadis ja röntgenuuringu tegemata jätmine esimesel visiidil. *Äärmuslikult pikenenud tervishoiusüsteemi viivituse* riskitegurid olid bakterierituse puudumine röga äigepreparaadis, röntgenuuringu tegemata jätmine esimesel visiidil ja patsiendi vanus üle 60 aasta.

Pikenenud tervishoiusüsteemi viivitus oli lühem mitte-eestlastel, *äärmuslikult pikenenud tervishoiusüsteemi viivitus* oli lühem mitte-eestlastel, töötutel ja tervisekindlustuseta isikutel. *Pikenenud ega äärmuslikult pikenenud patsiendi viivitusel* ei leitud seost arsti erialaga, kelle juurde patsient esimesena pöördus, uuritavate perekonnaseisu, soo, haridustaseme ega võimalike kontaktidega TB-haigega.

Patsientide tegevus sümptomite leevendamiseks

Uuritavate küsitlus nende tegevuse kohta sümptomite leevendamiseks enne arsti poole pöördumist selgitas, et 133 (71,9%) patsienti ootas sümptomite mööduмist iseeneslikult, 86 (46,5%) puhkas rohkem, 50 (27,0%) kasutas ravimeid, mis on kättesaadavad arsti retseptita, 16 (8,6%) vähendas suitsetamist ning 29 (15,7%) ja 4 (2,2%) vastavalt kas suurendasid või vähendasid oma alkoholitarbimist.

Arsti poole pöördumise viivituse põhjused

Enamik uuritavatest, 165 (89,2%), esitasid vähemalt ühe põhjuse, miks nad kohe pärast sümptomite tekkimist arsti poole ei pöördunud. Enamik uuritavatest, 131 (70,8%), ootasid, et sümptomid mööduksid iseenesest. Kolmandik, 56 uuritavat (30,3%), põhjendas viivitust haiguskindlustuse puudumisega, 40 (21,6%), kartis haiglaravi, 38 (20,5%) arvas, et visiit arsti juurde on kallis, 13 (7,0%) hirmutas võimalik töökoha kaotus.

JÄRELDUSED

1. Kopsuvälise TB haigestumus Eestis 1991.–2000. a. suurenes statistiliselt oluliselt vähem kui kopsutuberkuloosi haigestumus, seetõttu vähenes 10 aasta jooksul kopsuvälise TB suhteline sagedus.
2. Sarnaselt kopsutuberkuloosiga suurenes suhteliselt lühema latentsiperioodiga tekkivate kopsuvälise TB paikmete (rindkeresiseste lümfisõlmede TB ja tuberkuloosne pleuriit) sagedus. Selline olukord on iseloomulik infektsiooni laialdasele levikule ühiskonnas 10 aasta jooksul.
3. Kopsutuberkuloosi väikevormide osakaal kopsutuberkuloosi kõigi juhtude seas vähenes vaatlusperioodil, mis viitab kopsutuberkuloosi hilinenud diagnoosimisele.
4. Kopsuvälise TB sagedus kõigi TB juhtude hulgas oli suurim lastel ja see vähenes koos vanuse tõusuga. Kopsuväliste paikmete esinemissageduses ilmnesid ealised erinevused. Lümfisõlmede TB diagnoositi kõige rohkem lastel, tuberkuloosset pleuriiti vanuses 15–44 aastat, urogenitaalse TB ning luu- ja liigesetuberkuloosi sagedus suurenes koos vanusega.
5. Tuberkuloosne pleuriit, luu- ja liigesetuberkuloos, urogenitaalne TB ja lümfisõlmede TB moodustasid üle 90% kõigist kopsuvälistest paikmetest nii meestel kui naistel. Perifeersete lümfisõlmede TB esines sagedamini naistel, kuid intratorakaalsete lümfisõlmede TB sageduses ei olnud olulist soolist erinevust.
6. Bakterioloogiliselt ja/või histoloogiliselt kinnitunud haigusjuhtude sagedus oli kopsuvälise TB puhul oluliselt väiksem kui kopsutuberkuloosi korral. Kopsuvälised paikmed erinesid üksteisest haiguse mikrobioloogilise/ histoloogilise kinnituse poolest, sagedus oli suurem urogenitaalse TB ja pleura TB korral, väiksem rindkeresiseste lümfisõlmede TB ning luu- ja liigesetuberkuloosi korral.
7. *Patsiendi viivitus* oli Lõuna-Eestis pikem, kui on näidanud mitme mujal läbi viidud uuringu andmed. *Tervishoiusüsteemi viivitus* seevastu ei erinenud mujal leitust ja selle võib hinnata optimaalseks.
8. Perearstid suudavad edukalt diagnoosida TB, sest tervishoiusüsteemi viivitus ei sõltunud sellest, millise eriala arsti poole patsient esimesena pöördus.
9. *Pikenenud patsiendi viivituse ja äärmusliku patsiendi viivituse* riskitegurid olid meessugu ja elamine maapiirkonnas, kuid riskiteguriks ei osutunud võõrrahvus ega töötus.
10. *Pikenenud tervishoiusüsteemi viivituse* ja *äärmusliku tervishoiusüsteemi viivituse* riskitegurid olid patsiendi vanus üle 60 aasta, röntgenuuringu tegemata jätmine esimesel visiidil ja TB väikevormidele iseloomulikud köha puudumine ja bakterierituse puudumine röga äigepreparaadis. Töötutel, ravikindlustuseta isikutel ja mitte-eestlastel oli *tervishoiusüsteemi viivitus* isegi lühem.

11. Haigussümptomid esinesid enamikul uutest kopsutuberkuloosihaigetest.
    Kõige sagedamini esinevad kopsutuberkuloosi sümptomid ja samas ka kõige sagedasemad esimesed haigussümptomid olid köha, väsimus ja palavik.
    Patsiendi viivitus oli kõige lühem, kui esimese sümptomina tekkis palavik või valud rindkeres, ning kõige pikem, kui esimesed sümptomid olid vere-köha ja köha. Köha ei olnud patsiendi meelest tõsine sümptom.
12. Tuberkuloosi oskas sümptomite põhjusena kahtlustada ainult väike osa patsientidest. Patsientide tegevus sümptomite leevendamiseks enne arsti poole pöördumist seisnes peamiselt ootamises, et sümptomid mööduvad iseenesest; harvem kasutati ravimeid, mis on kättesaadavad arsti retseptita. Haiged põhjendasid viivitust arsti poole pöördumisel järgmiselt: lootsid, et sümptomid mööduvad iseenesest, puudus haiguskindlustus, kartsid, et visiit arsti juurde on kallis, ja kartsid kuulda diagnoosi. Asjakohase teabe puudumine võib olla põhjuseks, miks patsiendi viivitus Lõuna-Eestis oli pikem, kui näitavad teistes riikides tehtud uuringute andmed.

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11. PUBLICATIONS

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Kuulumine erialastesse organisatsioonidesse:
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