Respiratory tuberculosis incidence and mortality in Estonia: 30-year trends and sociodemographic determinants

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SUMMARY

OBJECTIVE: To explore time trends in the incidence and mortality of respiratory tuberculosis (TB) over a 30-year period in Estonia, and to evaluate disease disparities according to sex, age, ethnicity and education.

DESIGN: Data from the TB Register and the Causes of Death Register were used to assess time trends in age-standardised incidence and mortality rates. The effect of sociodemographic characteristics on TB risk was modelled using Poisson regression around three population censuses.

RESULTS: Respiratory TB incidence and mortality decreased in males and were stable in females in 1987–1991, after which the rates increased sharply in both sexes until 1998 and decreased steadily afterwards. Multidrug-resistant TB (MDR-TB) incidence rose in males until 1998 and in females until 2002, and then started to fall. The incidence of TB and human immunodeficiency virus (HIV) coinfection in males increased until 2007 and decreased thereafter. Less educated people and non-Estonians had a significantly higher relative risk of respiratory TB.

CONCLUSION: Estonia, one of the countries most affected by TB in the World Health Organization European Region, has made considerable progress in reducing the risk of respiratory TB, TB-HIV and MDR-TB. Continuing education- and ethnicity-related disparities in TB risk remain a concern.

KEY WORDS: education; ethnicity; Poisson models; risk factors; trend analysis

IN 1993, THE WORLD HEALTH Organization (WHO) proclaimed tuberculosis (TB) a global health emergency.1 Despite the progress made in diagnosis and treatment, TB remains a global health problem, with 10.4 million new cases and 1.7 million deaths worldwide every year.2 TB is also an important public health issue in the WHO European Region, where incidence and mortality vary widely by country.3

In 2007, the WHO identified 18 high-priority countries (HPCs) most affected by tuberculous infection among the 53 countries of the region: Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, the Republic of Moldova, Romania, the Russian Federation, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan.4 These 18 countries account for 85% of new cases, 98% of TB and human immunodeficiency virus (HIV) co-infection, 99% of multidrug-resistant TB (MDR-TB) cases and 88% of deaths due to TB in the region.3

The Republic of Estonia (in 2018, population 1.3 million, 52.9% women) belongs to the aforementioned HPCs, meaning that national TB control efforts should be concentrated on drastically reducing the TB burden. In response to the unexpected rise in TB incidence and mortality caused by profound social and economic destabilisation in the early 1990s,5 the first National Tuberculosis Control Programme (NTP) was outlined in 1997.6 The programme contributed to the modernisation of the TB surveillance system. In addition, the electronic Estonian Tuberculosis Register (ETR) was established in the same year. Since 2013, TB control activities have been integrated into the National Health Plan. The ETR provides data to the Statistical Office of Estonia, the Health Statistics and Health Research Database of the National Institute for Health Development, the WHO and the European Centre for Disease Prevention and Control, thus participating in a global TB surveillance system.2,4 In addition to routine use of ETR statistics, several studies have investigated inequalities in TB incidence and mortality.7–9

The present study is a part of a comprehensive research project focused on population health determinants and maximisation of the use of health databases. The objectives of the study were to explore time trends in the incidence and mortality of respiratory TB over a 30-year period in Estonia and...
to evaluate disease disparities according to sex, age, ethnicity and education.

**STUDY POPULATION AND METHODS**

Here, we report bacteriologically and histologically confirmed (International Classification of Diseases [ICD] 10 A15), and bacteriologically or histologically unconfirmed (ICD-10 A16) respiratory TB incidence and mortality in the adult population (age ≥15 years) in Estonia for the longest period for which data were available, 1987–2016. Incidence (new cases) data were extracted from the ETR, which is a population-based, countrywide register. As a mandatory TB case notification system existed in Estonia long before the ETR was founded, the register contains retrospectively entered individual records of new TB cases diagnosed in 1987–1996. Individual records in the ETR contain personal identity information, diagnosis, comorbidity and treatment data, and related sociodemographic factors such as ethnicity, educational level, marital status and employment status. Ethnicity in Estonia is self-determined and information is included in TB notifications. New TB cases among non-residents of Estonia were excluded from the dataset (8 males).

Death records with respiratory TB as the underlying cause of death were obtained from the Estonian Causes of Death Register. Over the study period, three classifications for coding cause of death were in use: an abridged Soviet version based on ICD-9 (respiratory TB code 9) during 1988–1993, ICD-9 (011–012) during 1994–1996 and the ICD-10 in 1997–2016. Twenty-four unidentified deaths (21 males, 3 females) with no information on date of birth were omitted from the analysis.

Age-standardised incidence rates (ASIR) of TB, MDR-TB (1995–2016) and TB-HIV (2001–2016), and mortality rates (ASMR) for TB per 100 000 person-years, were calculated applying the European standard population. Time trends in ASIR and ASMR were visualised with a line graph, and 3-year moving overlapping time periods were used to smooth short-term fluctuations caused by the small number of TB cases and deaths. Linear regression models with log-transformed ASIRs and ASMRs by year were fitted to quantify the average annual percentage change (AAPC) of these rates in three periods, 1987–1991, 1991–1998 and 1998–2016, with expected turning points in trends in 1991 (dissolution of the Soviet Union and subsequent poor TB control) and 1998, when the NTP came into force.

We used Poisson regression models to estimate male:female rate ratios (RRs) for incidence and mortality. Models were adjusted for age at diagnosis or death (5-year age groups) and year of diagnosis or death. AAPCs and RRs are presented with 95% confidence intervals (CIs). To assess the effect of sociodemographic characteristics on TB incidence and mortality risk, RRs were modelled using Poisson regression around three population censuses with the following dates: 12 January 1989 (TB cases and deaths 1987–1990), 31 March 2000 (1998–2001) and 31 December 2011 (2010–2013). We analysed only males to have a sufficient number of cases and deaths for the distribution of age, ethnicity and education. Age was restricted to 20–69 years, as the number of TB cases outside this age range was relatively small. Age group (45–69 years vs. 20–44 years), ethnicity (non-Estonian vs. Estonian) and education (basic or less vs. higher or secondary) were included in the models. TB cases and deaths with unknown ethnicity or education were excluded from the analysis: 110 TB cases and 3 deaths in 1987–1990; 14 TB cases and 18 deaths in 1998–2001; 14 TB cases and 2 deaths in 2010–2013.

The statistical package Stata v14 was used for modelling (StataCorp LP, College Station, TX, USA).

**Ethics statement**

Ethics approval was not required, as only routinely collected and anonymised secondary data from the ETR and the Estonian Causes of Death Register were used.

**RESULTS**

From 1987 to 2016, 11 440 new respiratory TB cases (8198 males, 3242 females) and 2034 respiratory TB deaths (1693 males, 341 females) were registered in the adult population of Estonia (508 064 males and 595 199 females in 2016). The frequency distribution of new cases and deaths according to various characteristics is given in Table 1.

Age-specific incidence and mortality curves in males illustrate the rapid rise in rates until 50 years of age. In females, after the initial increase in incidence, rates started to decline after age 30 years; mortality showed two periods of increase—one until age 40 years and another after 60 years (Figure 1).

In the first period analysed, the ASIR decreased by on average 6.5% per year, from 47.5 in 1987 to 38.0/100 000 in 1991 in males, and fluctuated without a clear trend between 9.8 and 12.7/100 000 in females (Table 2, Figure 2). A sharp increase began after that (AAPC 14.2 and 14.1 in males and females, respectively), with a peak in 1998, at an ASIR of 97.8/100 000 in males and 32.8/100 000 in females. A steady decline thereafter resulted in an ASIR of 21.3/100 000 (AAPC −7.9) in males and 6.1/100 000 (AAPC −8.9) in females in 2016.

In 1995–2016, 11.1% of all new cases among males and 10.6% among females were MDR-TB. Male MDR-TB incidence increased considerably until 1998 (ASIR increase from 3.2 to 10.9/
100 000) and decreased thereafter (ASIR 2.4/100 000 in 2016). An upward trend among females until the highest point in 2002 did not reach significance (ASIR from 0.7 to 3.5/100 000); a later decline was noteworthy (ASIR 0.9/100 000 in 2016) (Table 2, Figure 2).

In 2001–2016, 8.7% of males and 5.4% of females had TB-HIV co-infection at their first diagnosis of TB. The incidence of TB-HIV in males had an extremely upward trend until 2007 (ASIR from 0.9 to 6.0/100 000); the subsequent decrease was –7.5% per year (ASIR 3.4/100 000 in 2016). The trend analysis for females was not meaningful due to the small number of cases (Table 2, Figure 2).

The mortality curve resembled that of incidence, except for an increasing trend in males in 1987–1991, when the ASMR rose from 7.4 to 10.3/100 000 (AAPC 9.0). In that period, TB mortality in females was low and stable, remaining between 0.8 and 1.1/100 000 (Table 2, Figure 2). The highest mortality was observed at 24.2/100 000 in males in 1998 and at 4.4/100 000 in females in 1999. From 1991 to 1998, the ASMR increased 11.3%/year in males and 18.3%/year in females. The subsequent fall in ASMR was rapid, reaching 2.3/100 000 (AAPC –13.7) in males and 0.4/100 000 (AAPC –12.7) in females in 2016.

Respiratory TB incidence in males exceeded that in females by a factor of three (male:female incidence RR 3.05, 95%CI 2.93–3.18); males had seven-fold greater mortality (male:female mortality RR 7.17, 95%CI 6.38–8.06). A separate analysis of sociodemographic disparities among males indicated a shift to the older age group in incidence of respiratory TB: the relative risk (age 45–69 vs. 20–44) increased from 0.75 (1987–1991) to 4.43 (1987–1990) to 1.43 (2010–2013). Older males were at a greater risk of dying due to TB, and the risk grew sharply in the latest period (Table 3). There was a strong effect of education on TB incidence and mortality: the relative risk (basic or lower vs. secondary or higher educational level) varied from 2.01 (1998–2001) to 3.30 (2010–2013) for incidence and from 3.17 (1998–2001) to 5.93 (1987–1990) for mortality. Inequality by ethnicity (non-Estonians vs. Estonians) widened with time; it was not apparent during the Soviet period (1987–1990), and was highest in the last period (2010–2013): the relative risk increased from 0.97 to 2.10 for incidence and from 1.05 to 2.77 for mortality.
DISCUSSION

Our study indicates that in Estonia, the ASIRs and ASMRs of respiratory TB decreased in males and were stable in females during 1987–1991, then increased sharply in both sexes until 1998 and decreased steadily thereafter. MDR-TB incidence rose in males until 1998 and in females until 2002, and afterwards started to fall. TB-HIV incidence in males increased until 2007 and subsequently decreased. Less educated individuals and non-Estonians had a significantly higher relative risk of respiratory TB.

Time trends in TB occurrence reflected the numerous economic, technological, population, medical and other changes. The level of TB incidence and mortality until 1991 was achieved through Soviet TB control programmes, including the TB dispensary system. At that time, HIV had not yet contributed largely to the risk of TB. The collapse of the Soviet Union in the 1990s led to the deterioration of the economy and the health care system, which had an

Figure 1  Incidence and mortality rates of respiratory tuberculosis by 5-year age groups, Estonia, 1987–2016. py = person-years.

Figure 2  TB ASIR and ASMR in the adult population (≥15 years) at 3-year periods, Estonia, 1987–2016. ASIR = age-standardised incidence rate; ASMR = age-standardised mortality rate; py = person-years; MDR-TB = multidrug-resistant TB; TB = tuberculosis; HIV = human immunodeficiency virus.
immediate impact on the spread of TB. The previous Soviet model of TB services no longer functioned, and a sharp increase in TB incidence and mortality followed.

As noted elsewhere, the gradual improvements in the social and economic situation in Estonia made it possible to create a quality-assured laboratory network for mycobacteriology, centralise the procurement and distribution of anti-tuberculosis drugs, implement directly observed treatment and ensure countrywide access to second-line drugs. These changes, together with the supportive supervision of TB services and the training of health care staff to manage TB patients, influenced the decline of TB incidence and mortality from 1998.

The ETR plays a key role in national TB control. All physicians who diagnose TB or treat TB patients are required to report TB cases and treatment outcomes in the register. Independently, mycobacteriological laboratories are obliged to report monthly data of analysed samples using smear, culture and drug susceptibility testing results to ensure data completeness. The ETR is designed as a person-based register, in which observation units are new TB cases, relapse cases and all treatment episodes. To avoid double registration of cases, the register has verification systems based on unique personal identification numbers given to all residents of Estonia. In this context, the serious problem of underreporting of cases in high-incidence countries does not concern the TB control activities in Estonia.

In terms of the WHO 2016 estimates of TB incidence and mortality rates in 217 countries/territories, Estonia falls in the seventh decile. As shown in our study, there were wide sex differences in respiratory TB incidence. Taking all forms of TB together, female (but not male) populations with recent rates under 10/100 000 can be regarded as low incidence. During the last 18 years, the number of new cases has decreased rapidly, and Estonia currently has the lowest TB incidence and second lowest TB mortality among the 18 HPCs.

The high levels of MDR-TB can be explained by the high prevalence of the Mycobacterium tuberculosis Beijing genotype, which was introduced into Estonia.

### Table 3 Respiratory TB incidence and mortality RR with 95%CIs among adult males aged 20–69 years in Estonia by sociodemographic characteristics based on the 1989, 2000 and 2011 population censuses

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<td>Basic/primary</td>
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* Adjusted for other sociodemographic characteristics in the table.
† Mainly Russians (respectively 74%, 78% and 82% of non-Estonians aged 20–69 years in 1989, 2000, 2011).

TB = tuberculosis; RR = rate ratio; CI = confidence interval; py = person-years; aRR = adjusted RR.
with the mass influx of people, particularly from Russia,\textsuperscript{20–22} when, during 1934–1989, the proportion of population of foreign origin increased from 1\% to 34\%.\textsuperscript{23} As explained elsewhere,\textsuperscript{22} the Beijing B0/W148 cluster, which began to circulate in Estonia in the 1990s, has the most prominent role in the development of MDR-TB, and its increasing prevalence represents a serious obstacle to TB control in the country.

In terms of the relative frequencies of TB-HIV co-infection, Estonia ranks fifth in the WHO European Region.\textsuperscript{3} TB-HIV incidence is also demonstrating a decreasing trend. The first HIV case in Estonia was diagnosed in 1988.\textsuperscript{24} HIV testing has been performed in the TB services since the early 1990s; however, at that time, HIV-positive status, but not HIV-negative status, was recorded. One HIV-positive case was diagnosed among TB patients in 1997, 1999 and 2000. Since 2001, the ETR includes high coverage (over 90\% of TB cases tested) and representative data on TB-HIV, and, since 2009, data on HIV testing dates, antiretroviral therapy coverage, CD4 counts and viral load.

The spectrum of sociodemographic and lifestyle risk factors for PTB is wide, and includes low education levels, unemployment, poverty, homelessness, history of incarceration, smoking, alcohol abuse and illicit drug use.\textsuperscript{25–27} In Estonia, in a matched case-control study,\textsuperscript{28} PTB was found to be more common among men of working age; low socio-economic status, smoking and heavy alcohol consumption were associated with TB. In another study, higher respiratory TB mortality was related to older age, lower educational level and non-Estonian ethnicity.\textsuperscript{9}

In the present study, all sociodemographic characteristics studied among males (older age, non-Estonian ethnicity, lower education) were associated with higher TB incidence and risk of mortality. In terms of incidence, older age (45–69 years vs. 20–44 years) was a risk factor only in 2010–2013, demonstrating a greater decrease in the number of new cases over time among males of younger ages. A permanently higher TB death risk in the older age group in the three periods may show that younger patients had better TB treatment outcomes.

The increased risk of TB among non-Estonians, predominantly Russians, has been related to a higher prevalence of risk factors in this group. Compared with Estonians, non-Estonians had lower income, higher unemployment and more precarious living conditions; this population group has also included more manual workers, heavy smokers and consumers of strong alcohol.\textsuperscript{29–31} The educational disparities observed in risk of TB are similar to those documented elsewhere,\textsuperscript{8,32} and reveal the importance of education in shaping individuals’ professional life and health behaviour.

With the progress made, Estonia has the opportunity to become a low TB incidence country (<10/100 000) and then to move towards TB elimination. In accordance with the WHO vision, the challenge for each country to enter the TB pre-elimination phase (<1/100 000) involves a number of actions. The WHO’s proposed strategic framework envisages eight priority action areas,\textsuperscript{33} including political commitment to regulate TB case registration and treatment outcome monitoring, optimisation of the care of patients with MDR-TB, addressing vulnerable population groups and migrants, ensuring continued surveillance of TB patients, and financial support for clinical and epidemiological research.

The main strength of our study was the ability to use the countrywide ETR, which has become instrumental in the implementation of the NTP. The quality of the ETR relies heavily upon direct online access to the Population Register, linkage to the Causes of Death Register and cross-checks with regional TB services.

The study had some limitations. First, TB diagnostic criteria and registration principles have changed over time. Although TB case definitions and notification rules today are consistent with WHO guidelines, the same was not true years ago. During the Soviet period, only new TB cases were notified; notification of relapses started in 1995, and that of other retreatment cases started in 2001. TB cases in prisons were incorporated into the register as of 1998, and retrospectively for the period 1995–1997. All cases diagnosed post mortem have been included in the ETR since 2008. TB incidence before 2008 may thus have been underestimated.

Second, for retrospectively entered cases from 1987 to 1996, the date a new TB case was recorded in any register was taken as the date of diagnosis if other, more relevant dates were not available. It may be assumed that the difference between these two dates could range from some days to some months. This discrepancy should be addressed in TB survival studies, if initiated. Third, the small number of TB cases among females meant that part of our analysis had to be restricted to males only. However, we feel that, in general, our study was statistically robust. Fourth, some earlier deaths may have been mistakenly attributed to TB due to coding errors. If TB was mentioned on the death certificate, the disease was selected as the underlying cause of death, even if it was not active TB. This issue has also been a problem elsewhere.\textsuperscript{34,35} Finally, some HIV deaths may have been reported on death certificates as deaths due to TB.\textsuperscript{8}

In conclusion, Estonia, one of the countries most affected by TB in the WHO European Region, has made considerable progress in reducing the risk of respiratory TB, MDR-TB and TB-HIV. Persisting education- and ethnicity-related disparities in risk of TB, however, remain a concern.
Acknowledgements

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Conflicts of interest: none declared.

References


OBJECTIF : Explorer les tendances dans le temps de l’incidence et de la mortalité de la tuberculose (TB) pulmonaire sur une période de 30 ans en Estonie et évaluer les disparités de la maladie par sexe, âge, ethnicité et niveau d’instruction.

SCHEMA : Nous avons utilisé les données du registre TB et du registre des causes de décès afin d’évaluer les tendances dans le temps des taux d’incidence et de mortalité standardisés sur l’âge. L’impact des caractéristiques sociodémographiques sur le risque de TB a été modélisé par régression de Poisson autour de trois recensements de population.


CONCLUSION : L’Estonie, un des pays les plus affectés par la TB dans la région Europe de l’Organisation Mondiale de la Santé, a fait des progrès considérables en diminuant le risque de TB pulmonaire, de TB-VIH et de TB-MDR. La persistance de disparités du risque de TB liées au niveau d’instruction et à l’ethnicité reste préoccupante.