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Gafar, Fajri; Van't Boveneind-Vrubleuskaya, Natasha; Akkerman, Onno W.; Wilffert, Bob; Alffenaar, Jan-Willem C.

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Early View

Original article

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Nationwide analysis of treatment outcomes in children and adolescents routinely treated for tuberculosis in The Netherlands

Fajri Gafar,^{1*} Natasha van't Boveneind-Vrubleuskaya,^{2,3*} Onno W. Akkerman,^{4,5} Bob Wilffert,^{1,2} Jan-Willem C. Alffenaar^{2,6,7}

1. University of Groningen, Groningen Research Institute of Pharmacy, Unit of PharmacoTherapy, -Epidemiology, and -Economics, Groningen, The Netherlands.
2. University of Groningen, University Medical Center Groningen, Department of Clinical Pharmacy and Pharmacology, Groningen, The Netherlands.
3. Department of Public Health TB Control, Metropolitan Public Health Services, The Hague, The Netherlands.
4. University of Groningen, University Medical Center Groningen, Department of Pulmonary Diseases and Tuberculosis, Groningen, The Netherlands.
5. University of Groningen, University Medical Center Groningen, Tuberculosis Center Beatrixoord, Haren, The Netherlands.
6. University of Sydney, Faculty of Medicine and Health, School of Pharmacy, Sydney, Australia.
7. Westmead Hospital, Sydney, Australia

*FG and NBV Contributed equally to this manuscript

Corresponding author:

Fajri Gafar

University of Groningen,

Groningen Research Institute of Pharmacy,

Unit of Pharmacotherapy, -Epidemiology and -Economics,

Antonius Deusinglaan 1 (room: 3214.0450),

9713 AV Groningen, The Netherlands,

Tel: +31 50 36 32476

E-mail: f.gafar@rug.nl; and fajri.gafar@gmail.com

Take-home message:

High success rates for TB treatment were achieved in children and adolescents in The Netherlands. To further optimize care in this population, several risk factors particularly associated with mortality and lost to follow-up have been identified.

Running title:

TB treatment outcomes in children and adolescents in The Netherlands.

ABSTRACT

Background: As a vulnerable population, children and adolescents with tuberculosis (TB) are faced with many challenges, even for those who live in low TB incidence countries. We aimed to evaluate factors associated with TB treatment outcomes allowing more focused interventions to support this population once diagnosed.

Methods: A retrospective cohort study using a nationwide surveillance database was performed in children and adolescents (0-18 years) treated for TB in The Netherlands from 1993-2018. Logistic regression analyses were used to estimate adjusted odds ratios (aOR) for associated factors of mortality and lost to follow-up (LTFU).

Results: Among 3253 eligible patients with known outcomes, 94.4% (95.9% children and 92.8% adolescents) were cured or completed treatment, 0.7% died during treatment and 4.9% were LTFU. There were no reported treatment failures. Risk factors of death included children aged 2-4 years (aOR=10.42), central nervous system TB (aOR=5.14), miliary TB (aOR=10.25), HIV coinfection (aOR=8.60), retreated TB cases (aOR=10.12), and drug-induced liver injury (aOR=6.50). Active case-finding was a protective factor of death (aOR=0.13). Risk factors of LTFU were adolescents aged 15-18 years (aOR=1.91), illegal immigrants (aOR=4.28), urban domicile (aOR=1.59), unknown history of TB contact (aOR=1.99), drug-resistant TB (aOR=2.31), single adverse drug reaction (ADR) (aOR=2.12), multiple ADRs (aOR=7.84) and treatment interruption >14 days (aOR=6.93). Treatment in recent years (aOR=0.94) and supervision by public health nurses (aOR=0.14) were protective factors of LTFU.

Conclusion: Highly successful treatment outcomes were demonstrated in children and adolescents routinely treated for TB. Special attention should be given to specific risk groups to improve treatment outcomes.

Key words: Tuberculosis, treatment outcome, mortality, lost to follow-up, children, adolescent.

INTRODUCTION

Tuberculosis (TB) is a major global health problem with an estimated 1 million children who developed TB worldwide in 2017 [1]. Childhood TB has historically been given low priority in most national programmes because it contributes little to disease transmission. Similarly, adolescents are also faced with many challenges as they have been neglected in TB surveillance even when they suffer from a significant burden of the disease [2, 3]. Since the World Health Organization (WHO) published 10 key actions in 2013 as the first roadmap for childhood TB [4], significant progress has been made but gaps still remain especially on age- and disease-related challenges such as young children (<5 years), adolescents (10-19 years), TB/HIV coinfection, and multidrug-resistant TB (MDR-TB). The 2018 WHO roadmap brings new hope of accelerating efforts towards ending TB in children and adolescents by ensuring them to receive high priority in all TB prevention and control activities [5].

As one of the top ten causes of death, childhood TB is a silent killer with the risk of mortality being particularly high in under-five children and HIV co-infected children not receiving antiretroviral therapy (ART) [6, 7]. In low-incidence countries like The Netherlands, TB elimination requires extensive but focused screening and prevention as the patients become more concentrated in certain vulnerable and high-risk groups such as the poor, immigrants, asylum seekers, homeless, prisoners, alcohol or drug addicts, and people living with HIV/AIDS [8]. Management of childhood and adolescent TB is still a pressing challenge even for low-incidence countries, particularly due to the lack of child-friendly drug formulations, difficulties in diagnosis and treatment of latent TB infection (LTBI) [9].

Few studies with large cohorts of children mostly from high-incidence settings in Africa have reported factors associated with TB treatment outcomes in children [10–14]. However, most of the variables analysed in these studies were relatively limited to demographic and clinical characteristics. Other potential confounders such as vaccination status, types of case-finding, drug-susceptibility of the TB strains, and other clinical-, bacteriological- and treatment-related factors have not been fully evaluated. Related data in both children and adolescents from low-incidence countries is also lacking. In this context,

our study aimed to evaluate treatment outcomes and associated factors in children and adolescents routinely treated for TB in The Netherlands. This would allow for appropriate interventions to optimize TB care in this vulnerable population.

METHODS

Study design and data sources

This retrospective cohort study was performed using surveillance data obtained from the Netherlands Tuberculosis Register (NTR). The NTR is a nationwide database for patients with TB and LTBI, managed by the Dutch National Institute for Public Health and the Environment (RIVM) in collaboration with 25 departments of the Municipal Public Health Services (MPHS) and the Royal Netherlands Tuberculosis Association (KNCV). Since 1993, data on disease notification, demographics, clinical, bacteriological, and treatment characteristics are recorded by the MPHS in all TB patients.

Study population

All children and adolescents (0-18 years) treated for TB between January 1993 and December 2018 were included in this study. Patients in ongoing treatment with incomplete data on treatment outcomes were excluded.

Data collection

The following individual data with anonymous identifiers were obtained from the NTR on 22 May 2019: (1) demographics (year of diagnosis, age, gender, native/foreign-born, WHO region of birth, immigrant status, and area of living); (2) TB notification and clinical characteristics (types of case-finding, history of TB contact, travel history in TB endemic area, site and localisation of TB, cavitary TB, Bacillus Calmette-Guerin (BCG) vaccination, TB symptoms, patient's and doctor's delay in diagnosis and treatment, and comorbidity); (3) bacteriological characteristics (acid-fast bacilli (AFB) smear microscopy, mycobacterial culture, and drug susceptibility testing (DST)); and (4) treatment characteristics (previous history of TB/LTBI treatment, daily/intermittent dosing, presence of adverse drug reactions (ADRs), drug-induced liver injury (DILI), treatment interruption >14 days, hospitalisation,

treatment supervision by public health nurses (PHNs) and implementation of directly observed therapy (DOT)).

Definitions

Age was generally divided into 2 groups: children <15 years and adolescents aged 15-18 years. The cut-off of <15 years for children was used to be consistent with the age category used for reporting TB surveillance data nationally and by the WHO [1]. The upper age limit of 18 years for adolescent TB was based on the definition used by the WHO European Region [15]. Active case-finding (ACF) was defined as the systematic screening for active TB cases in a predetermined high-risk group for TB, rather than waiting for patients who came on their own to the healthcare system because of TB symptoms (passive case-finding (PCF)). Pulmonary TB (PTB) included all forms of TB in the lungs, isolated tracheal or bronchus TB, laryngeal TB, and other specified respiratory TB. TB within other locations in the body than the lungs, including mediastinal lymphadenopathy, were classified as extrapulmonary TB (EPTB), which may have involved isolated EPTB or a combination of PTB and EPTB. Confirmed drug-susceptible TB (DS-TB) was defined as a susceptible result of DST for all first-line anti-TB drugs (isoniazid, rifampicin, pyrazinamide and ethambutol), while presumed DS-TB was defined as patients treated with first-line anti-TB drugs without sufficient information on DST. Patients with DST results of mono-resistant, poly-resistant, MDR, or XDR (extensively drug-resistant) were classified as confirmed drug-resistant TB (DR-TB). DILI due to anti-TB drugs was defined as an increased level of alanine aminotransferase >3x the upper limit of normal (ULN) in the presence of symptoms of hepatotoxicity or >5x the ULN in the absence of symptoms. Treatment supervision by PHNs was defined as supportive discussions with patients and their family to provide TB education and identification of obstacles that influence treatment adherence. DOT was defined as every dose of anti-TB drugs taken under direct observation for a period of time, provided by either PHNs or other selected third parties such as family members or home nursing services. Operational definitions for all variables are shown in Supplementary Table 1 [16, 17].

Outcomes

Treatment outcomes (cured, treatment completed, died, treatment failed, lost to follow-up (LTFU), and not evaluated (unknown outcomes)) were defined based on the Dutch national guidelines for TB programmes and generally in accordance with the current WHO guidelines (Table 1) [16, 18].

Data analysis

Associations of patient characteristics with mortality and LTFU were evaluated. First, patients who died during treatment were compared to those who were alive at the end of treatment regardless of whether they were cured, completed or failed treatment; this definition excluded LTFU and unknown outcomes. Second, LTFU patients were compared to those who achieved cure or completed treatment with or without evidence of treatment failure; this definition excluded death and unknown outcomes. Given the possibility of selection bias from the exclusion of particular patients in the first and second analyses, additional outcome classification was created assessing patients who achieved cure or completed treatment (favourable) compared to all other outcomes (unfavourable).

Univariate and multivariate logistic regression analyses were used to evaluate the association between candidate variables and treatment outcomes. All variables in the univariate analysis showing a trend towards association with each of the evaluated outcomes, and with a minimum number of 20 patients in any particular group of predictors, were eligible for inclusion in multivariate analysis and were selected using backward elimination. The final multivariate models retained all explanatory variables with a *P*-value <0.1. The Hosmer-Lemeshow test was used to evaluate the goodness-of-fit of the final models. The performance of the final models were measured by the area under the receiver operating characteristic (ROC) curve. Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) were used to estimate the association between explanatory variables and treatment outcomes. Statistical significance was accepted at *P*<0.05 whereas *P*-values of 0.05-0.10 were considered trends. All data were analysed with IBM SPSS Statistics version 25.0.

Ethics

Research approval was granted by the research committee of the NTR. As this was a retrospective study using routine data collected anonymously, ethics clearance and individual patient written informed consent were not required under Dutch law.

RESULTS

During a 26-year period from January 1993 to December 2018, 3442 TB cases in children and adolescents were notified: 46 patients in ongoing treatment were excluded. Of 3396 eligible patients (1764 (51.9%) children and 1632 (48.1%) adolescents), 1893 (55.7%) being male, 2017 (59.4%) were foreign-born and 1454 (42.8%) had pulmonary TB (PTB). Mycobacterial culture was performed in 2261 (66.6%) of the eligible patients with 1921 (56.6%) being culture positive and 340 (10%) culture negative. Of 1921 patients with culture-confirmed disease, 1610 (83.8%) had information on species. Of these, 1523 (94.6%) had *M. tuberculosis* and 87 (5.4%) had other *M. tuberculosis* complex. None of the patients were identified as nontuberculous mycobacterial infections. Most of the patients (2625 (77.3%)) were treated as presumed DS-TB, 591 (17.4%) as confirmed DS-TB and 180 (5.3%) as confirmed DR-TB (Table 2). Severe forms of TB (CNS or miliary TB) were notified in 100 (2.9%) of 3396 eligible patients: 33 (33%) received BCG vaccination and 44 (44%) were BCG-unvaccinated. Of 44 severe cases who were BCG-unvaccinated, 23 (52.3%) were children <5 years, 15 (34.1%) were children aged 5-14 years and the remaining 6 (13.6%) were adolescents.

By including both patients with known and unknown outcomes, overall success rates of 92.0% and 88.7% were shown in children and adolescents, respectively. Known outcomes were recorded in 3253 (95.8%) of 3396 eligible patients. Of these, success rates were shown in 95.9% children and 92.8% adolescents (Table 2). Annual success rates in children were constantly above 90% over the years from 1993-2018, and relatively higher compared to adolescents (Figure 1). LTFU was higher in adolescents (102 (6.5%)) than children (58

(3.4%). No treatment failure was reported and 22 (0.7%) of the total patients died during treatment (Table 2). Case fatality rates (CFR) for other sub-population are presented in Supplementary Table 2.

Our multivariate model showed that children aged 2-4 years had an increased odds of death compared to children aged 5-14 years (aOR: 10.42; 95% CI: 2.25-48.36). Positive associations with mortality were also shown in patients with central nervous system (CNS) TB (aOR: 5.14; 95% CI: 1.17-22.62), miliary TB (aOR: 10.25; 95% CI: 2.30-45.67), HIV coinfection (aOR: 8.60; 95% CI: 1.57-47.24), retreated TB cases (aOR: 10.12; 95% CI: 1.54-66.47) and those who developed DILI during therapy (aOR: 6.50; 95% CI: 1.09-38.71). The ACF was associated with lower odds of death compared to PCF (aOR: 0.13; 95% CI: 0.03-0.66) (Table 3). Patients with unknown history of TB contact, with unknown BCG status, who experienced TB symptoms or were hospitalised ≥ 1 week during treatment had a significant increased odds of death in univariate analysis but did not remain significant in multivariate analysis (Supplementary Table 3). Although unknown history of TB contact was not sustained in multivariate analysis as a predictor of mortality, it was significantly associated with higher odds of either patient's delay (aOR: 2.36; 95% CI: 1.46-3.80) or doctor's delay (aOR: 4.29; 95% CI: 2.48-7.42) compared to known TB contact history, adjusted for age, gender, smear microscopy and sites of TB.

Several factors were associated with higher odds of LTFU including adolescents (aOR: 1.91; 95% CI: 1.25-2.93), illegal immigrants (aOR: 4.28; 95% CI: 1.60-11.42), urban domicile (aOR: 1.59; 95% CI: 1.10-2.29), unknown history of TB contact (aOR: 1.99; 95% CI: 1.19-3.34), confirmed DR-TB (aOR: 2.31; 95% CI: 1.05-5.10), single ADR (aOR: 2.12; 95% CI: 1.18-3.83), multiple ADRs (aOR: 7.84; 95% CI: 3.55-17.33) and treatment interruption >14 days (aOR: 6.93; 95% CI: 2.72-17.63). Treatment in recent years (aOR: 0.94; 95% CI: 0.89-0.98) and treatment supervision by PHNs (aOR: 0.14; 95% CI: 0.07-0.29) were associated with lower odds of LTFU (Table 4). Being male and foreign-born were significantly associated with higher odds of LTFU in univariate analysis but not found statistically significant in multivariate analysis (Supplementary Table 4). However, our subgroup analysis

identified that male foreign-born adolescents had a significantly increased odds of LTFU compared to female foreign-born adolescents (aOR: 2.31; 95% CI: 1.30-4.10), adjusted for year of diagnosis, area of living, DST results, presence of ADRs, treatment interruption >14 days and treatment supervision by PHNs.

The following factors were associated with higher odds of unfavourable outcome: children <5 years (aOR: 1.58; 95% CI: 1.02-2.46), adolescents (aOR: 1.56; 95% CI: 1.11-2.19), illegal immigrants (aOR: 5.10; 95% CI: 2.15-12.10), unknown history of TB contact (aOR: 2.00; 95% CI: 1.30-3.07), miliary TB (aOR: 3.37; 95% CI: 1.42-8.03), multiple ADRs (aOR: 7.54; 95% CI: 3.56-15.99) and treatment interruption >14 days (aOR: 4.90; 95% CI: 2.10-11.42). Treatment supervision by PHNs was associated with lower odds of unfavourable outcome (aOR: 0.08; 95% CI: 0.05-0.15) (Table 5). Results of the univariate analysis for unfavourable outcome are presented in Supplementary Table 5.

DISCUSSION

An overall high success rate of 92.0% in children was recorded in our study although this included children with unknown outcomes. This is relatively comparable with studies of children from other low-incidence countries such as Australia (89.4%) and the United Kingdom (UK) (88.0%) [19, 20]. A high success rate was also recorded in adolescents: comparable data from other low-incidence countries is lacking. This underlines that adolescents are often neglected in TB surveillance reports [3, 5]. The low mortality rate of <1% in our study is similar to those reported in the UK and Australia [19, 20] but is lower compared to various reports from high-incidence countries in Asia and Africa (3-17%) [11–14]. Interestingly, a recent study from South Africa also reported less than 1% mortality rate in children; however, this number was probably higher as children with severe forms of TB admitted to hospital may have died before diagnosis or after diagnosis but prior to recording in the database [10].

Several risk factors of mortality are shown in our study including children aged 2-4 years, CNS TB, miliary TB, HIV coinfection, retreated TB cases and cases with DILI. Overall,

the increased risk of death in children under 5 years of age is consistent with those reported in a meta-analysis and a modelling study [6, 7]. However, in contrast to earlier findings from South Africa [10], our results did not confirm the risk of death in a subgroup of children <2 years. In children <2-3 years, the progression of primary infection into severe disease (CNS or miliary TB) is more frequent [21]. These severe forms of disease were associated with mortality in our study, independently from age of the patients. In high-incidence countries, BCG vaccination has been reported as a highly cost-effective intervention to prevent CNS TB and miliary TB [22]. In The Netherlands, BCG vaccination is only targeted to new-borns with a parent coming from a country with estimated TB incidence >50 per 100,000 population, and offered for immigrants <12 years with no evidence of BCG vaccination at pre-entry TB screening [23]. Notably, more patients with severe disease in our study were BCG-unvaccinated: half of them were <5 years of age. These results support the previous recommendation by Erkens et al to improve the coverage of BCG vaccination among eligible risk groups in The Netherlands [24].

The role of TB/HIV coinfection as a predictor of mortality in children is supported by various studies mostly from HIV-endemic settings [10–13]. For TB/HIV co-infected children taking antiretroviral therapy (ART), the risk of death is lower than children without ART [6]. In our cohorts, ART status was not completely clear because it was being recorded in the NTR only since 2016. Next, a recurrent episode of TB can be due to endogenous reactivation of indolent mycobacteria (relapse) or exogenous reinfection, and the latter can be caused by MDR *M. tuberculosis* strains [25]. Two patients with recurrent TB who died in our study were classified as non-relapse patients, one of which was treated for MDR-TB. It is possible that MDR-TB also plays a role in increasing the risk of mortality in recurrent TB.

DILI is one of the most frequent and serious ADRs during TB-therapy [26], and also reported as a predictor of prolonged TB treatment in a Dutch setting [27]. Although with a relatively lower rate of DILI in our study (1.8%) compared to other studies of children in Japan (8.1%) and Indonesia (15%) [28, 29], its clinical implication in increasing the risk of mortality should be taken seriously. Two studies from India and the UK also reported DILI as

a contributing cause of death in adult TB patients [30, 31], with the risk of mortality being even higher if accompanied by jaundice, ascites or encephalopathy [31]. Based on the current WHO guidelines for children, regular monitoring of liver function tests (LFTs) during TB-therapy is not mandatory and only recommended if liver tenderness, hepatomegaly, jaundice or early onset of vomiting occur during treatment [32]. Given that severe hepatotoxicity can develop in patients with asymptomatic DILI [33], regular monitoring of LFTs as suggested for adults undergoing TB therapy might also benefit children to improve treatment outcomes and to prevent mortality.

In The Netherlands, pre-entry LTBI screening is carried out for every immigrant and asylum seeker <18 years, and radiographic screening is recently suggested only in children between 12-17 years from a country with TB incidence ≥ 100 per 100,000 population [34]. The ACF interventions such as screening for immigrants and asylum seekers as well as source and contact investigations have proven useful in our study to prevent mortality compared to PCF. Given that unknown history of TB contact was also found as a risk factor of either patient's or doctor's delay, this highlights the benefits of advocating ACF for early diagnosis and early treatment (including preventive therapy), in order to prevent deterioration of the disease. A large randomised controlled trial (RCT) from Vietnam supports that ACF is a cost-effective intervention to increase TB case detection and to reduce all-cause mortality [35, 36]. A modelling study also reported that household contact investigations could substantially prevent both TB cases and mortality in children [37].

For LTFU, our study identifies the following risk factors: adolescent age, illegal immigrants, unknown history of TB contact, urban domicile, confirmed DR-TB, presence of ADRs and treatment interruption >14 days. The increased risk of LTFU in adolescents particularly in male foreign-born adolescents might be due to the lack of awareness of the special needs of this population [15]. To improve adherence in adolescents, appropriate interventions should be understood by considering their developmental and psychosocial issues, tailoring the treatment regimen and ensuring peer and family supports [38]. Implementation of DOT in our study was not statistically significant to prevent LTFU even in a

particular subgroup of adolescents. This is supported by a meta-analysis that poor adherence in TB treatment cannot be resolved by DOT intervention [39]. A recently published RCT from the UK reported that smartphone-enabled video-observed therapy (VOT) is more effective, preferable and cheaper than DOT for TB treatment observation [40]. In The Netherlands where internet connectivity is not an issue, VOT might also be relevant as an alternative to DOT, particularly for adolescents who have a high mobile-internet engagement. A new framework of digital health (e-health) as currently recommended by the WHO [41], might also benefit to ensure treatment adherence. Even though this e-health system has not been widely used in The Netherlands [23], it has great potential as a more patient-friendly intervention for therapy monitoring, particularly for high-risk groups and other individuals with complex confounders (e.g. patients living in urban areas or treated for DR-TB).

Since 2005, a central web-based TB surveillance system was introduced and laboratory data were matched with the NTR in real-time. These improvements might have contributed to the reduced number of LTFU cases in recent years. This is supported by our results that most of the LTFU cases (79%) were notified before 2005. The improved TB outcomes might also be related to the large number of stakeholders involved in TB control activities; from the MPHS, KNCV, RIVM, and other health professionals such as pulmonary physicians, paediatricians, TB control physicians, medical microbiologists, medical technicians and PHNs [23]. Our study confirms that treatment supervision by PHNs is a protective factor of LTFU as well as unfavourable outcome.

A particular strength of this study is a relatively wide range of variables included in the analysis from demographics to disease notification-, clinical-, bacteriological- and treatment-related factors. However, our study has several limitations that should be acknowledged. Due to the retrospective nature of the study using routine data, patient records were partly incomplete for some of the variables. Even though notification of TB is mandatory, the possibility of undernotification cases cannot be ruled out. Through a capture-recapture analysis, the adjusted undernotification of TB in 1998 was estimated to be 7.3% [42].

However, the completeness of notification is expected to have increased since 2005 when improvements were made to the NTR. The high proportion of patients with presumed DS-TB in our cohorts can be explained by these changes, given that 1139 (99%) of 1150 patients with culture-confirmed disease but did not have information on DST results were registered before 2005. Next, our database cannot distinguish between TB contact history with an infectious DR-TB and DS-TB case, and this may have led to misclassification of presumed DS-TB in some patients who should have been classified as presumed DR-TB. The low proportion of patients who died and were LTFU in our cohorts could also limit the statistical power of the study. Although the definition of mortality used in this study has followed the current WHO guidelines as all-cause mortality before starting or during the course of treatment [32], the differentiation of death due to TB from other causes along with post-mortem evidence could provide a more accurate characterisation of TB-related mortality. In addition, given the details on LFTs and clinical features of DILI are not registered in the NTR, further classification of symptomatic versus asymptomatic DILI cannot be presented.

In conclusion, this study demonstrates a high rate of successful treatment outcome in children and adolescents treated for TB in The Netherlands from 1993-2018. Specific risk groups for mortality, LTFU and unfavourable outcome have been identified for further development of early interventions to support these patients once diagnosed with TB.

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Author contributions

FG, NBV, BW and JWCA contributed to conception and design of the study. FG undertook data extraction and performed data analysis. FG, NBV, OWA, BW and JWCA interpreted the data. FG and NBV drafted the manuscript. BW and JWCA supervised the entire project. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript.

Conflict of interests

All authors do not have any conflict of interest to declare.

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Table 1. Treatment outcome definitions used in this study

Outcomes	Definition for DS-TB	Definition for DR-TB
Cured	A patient who had completed a full course of therapy or at least 80% of the prescribed doses with a confirmed culture-negative at the end of treatment.	A patients who had treatment completed without evidence of failure with three or more consecutive negative cultures taken at least 30 days apart after the intensive phase
Treatment completed	A patient who had taken all of the prescribed doses or at least 80% of them without any information of sputum culture at the end of treatment.	A patients who had treatment completed without evidence of failure, but no record that three or more consecutive cultures taken at least 30 days apart were negative after the intensive phase
Died	A patient who died for any reason before starting or during the course of treatment.	A patient who died for any reason during the course of treatment
Treatment failed	A patient whose sputum culture was positive after 5 months or later during treatment.	A patient who met one of the following criteria: 1) lack of conversion by the end of the intensive phase, 2) bacteriological reversion in the continuation phase after conversion to negative, 3) evidence of additional acquired resistance to fluoroquinolone or second-line injectable drugs, and 4) of adverse drug reactions requiring discontinuation of treatment.
Lost to follow-up	A patient who met one of the following criteria: treatment interruption for two consecutive months or more; treatment completion of less than 80% of the prescribed doses; treatment incompleteness of 6 months within the 9-month treatment period; or treatment incompleteness of 9 months within the 12-month treatment period.	A patient whose treatment was interrupted for 2 consecutive months or more.
Not evaluated (Unknown)	A patient for whom no treatment outcome (cured, treatment completed, died, treatment failed, and lost to follow-up) was assigned in the database. This included cases “transferred out” to another unit (country) with unknown treatment results.	A patient for whom no treatment outcome was assigned in the database. This included cases “transferred out” to another unit (country) with unknown treatment results
Treatment success	The sum of “cured” and “treatment completed”.	The sum of “cured” and “treatment completed”.

DR-TB, drug-resistant tuberculosis; DS-TB, drug-susceptible tuberculosis.

DR-TB comprised of mono-resistant TB (resistance to one first-line anti-TB drug only); poly-resistant TB (resistance to more than one first-line anti-TB drug other than isoniazid and/or rifampicin); multidrug-resistant TB (MDR-TB) (resistance to at least both isoniazid and rifampicin); extensively drug-resistant TB (resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin) in addition to MDR-TB); and rifampicin resistant TB (resistance to rifampicin with or without resistance to other anti-TB drugs). Source: [16, 18].

Table 2. Characteristics of children and adolescents treated for TB in The Netherlands

Characteristics	Total cases (n=3396)	<5 years (n=638)	5-14 years (n=1126)	15-18 years (n=1632)
Year of diagnosis				
1993-1998	1092 (32.2)	218 (34.2)	400 (35.5)	474 (29.0)
1999-2003	1005 (29.6)	173 (27.1)	270 (24.0)	562 (34.4)
2004-2008	485 (14.3)	110 (17.2)	177 (15.7)	198 (12.1)
2009-2013	398 (11.7)	79 (12.4)	151 (13.4)	168 (10.3)
2014-2018	416 (12.2)	58 (9.1)	128 (11.4)	230 (14.1)
Gender				
Male	1893 (55.7)	337 (52.8)	525 (46.6)	1031 (63.2)
Female	1503 (44.3)	301 (47.2)	601 (53.4)	601 (36.8)
Born in The Netherlands				
Yes	1350 (39.8)	502 (78.7)	522 (46.4)	326 (20.0)
No	2017 (59.4)	130 (20.4)	594 (52.8)	1293 (79.2)
Unknown	29 (0.9)	6 (0.9)	10 (0.9)	13 (0.8)
Site of TB				
PTB	1454 (42.8)	229 (35.9)	401 (35.6)	824 (50.5)
EPTB	1570 (46.2)	352 (55.2)	600 (53.3)	618 (37.9)
PTB + EPTB	372 (11.0)	57 (8.9)	125 (11.1)	190 (11.6)
Reason for TB investigation				
Presentation of TB symptoms	1582 (46.6)	178 (27.9)	478 (42.5)	926 (56.7)
Contact investigation	944 (27.8)	343 (53.8)	429 (38.1)	172 (10.5)
Screening high-risk groups	620 (18.3)	61 (9.6)	162 (14.4)	397 (24.3)
Others	35 (1.0)	12 (1.9)	11 (1.0)	12 (0.7)
Unknown	215 (6.3)	44 (6.9)	46 (4.1)	125 (7.7)
AFB smear microscopy (sputum or BAL)				
Negative	570 (16.8)	51 (8.0)	158 (14.0)	361 (22.1)
Non-cavitary TB	515 (15.2)	48 (7.5)	147 (13.0)	320 (19.6)
Cavitary TB	25 (0.7)	1 (0.1)	4 (0.3)	20 (1.2)
Positive	534 (15.7)	26 (4.1)	121 (10.7)	387 (23.7)
Non-cavitary TB	324 (9.5)	23 (3.6)	73 (6.5)	228 (14.0)
Cavitary TB	187 (5.5)	2 (0.3)	43 (3.8)	142 (8.7)
Unknown/ not done	2292 (67.5)	561 (87.9)	847 (75.2)	884 (54.2)
Mycobacterial culture				
Negative	340 (10.0)	60 (9.4)	130 (11.5)	150 (9.2)
Positive	1921 (56.6)	195 (30.6)	506 (44.9)	1220 (74.8)
Unknown/ not done	1135 (33.4)	383 (60.0)	490 (43.5)	262 (16.1)
Drug-susceptibility testing				
Confirmed DS-TB	591 (17.4)	46 (7.2)	144 (12.8)	401 (24.6)
Presumed DS-TB	2625 (77.3)	568 (89.0)	936 (83.1)	1121 (68.7)
Culture positive, DST unknown	1150 (33.9)	125 (19.6)	316 (28.1)	709 (43.4)
Culture negative or unknown	1475 (43.4)	443 (69.4)	620 (55.1)	412 (25.2)
Confirmed DR-TB	180 (5.3)	24 (3.8)	46 (4.1)	110 (6.7)
Mono/poly H	131 (3.9)	20 (3.1)	33 (2.9)	78 (4.8)
Mono/poly R	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)
Mono Z	14 (0.4)	3 (0.5)	4 (0.4)	7 (0.4)
MDR-TB	32 (0.9)	1 (0.2)	9 (0.8)	22 (1.3)
XDR-TB	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Treatment outcomes (uncorrected)				
Cured/completed	3071 (90.4)	577 (90.4)	1046 (92.9)	1448 (88.7)
Lost to follow-up	160 (4.7)	24 (3.8)	34 (3.0)	102 (6.3)
Failed	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Died	22 (0.6)	9 (1.4)	3 (0.3)	10 (0.6)
Not evaluated (unknown)	143 (4.2)	28 (4.4)	43 (3.9)	72 (4.4)
Treatment outcomes (corrected) [*]				
Total, n	3253	610	1083	1560
Cured/completed	3071 (94.4)	577 (94.6)	1046 (96.6)	1448 (92.8)
Lost to follow-up	160 (4.9)	24 (3.9)	34 (3.1)	102 (6.5)
Failed	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Died	22 (0.7)	9 (1.5)	3 (0.3)	10 (0.6)

Data are presented as number with percentages (%); AFB, acid-fast bacilli ; BAL, bronchoalveolar lavage; DST, drug-susceptibility testing; DSTB, drug-susceptible tuberculosis; DRTB, drug-resistant tuberculosis; EPTB, extra-pulmonary tuberculosis; H, isoniazid; HIV, human immunodeficiency virus; MDR-TB, multidrug-resistant tuberculosis; PTB, pulmonary tuberculosis; R, rifampicin; XDR-TB, extensively drug-resistant tuberculosis; Z, pyrazinamide.

^{*}Excluded patients with unknown outcomes.

Table 3. Final model for factors associated with mortality in children and adolescents treated for TB in the Netherlands

	Died (n=22)	Alive ^a (n=3071)	cOR (95% CI)	P-value	aOR (95% CI)	P-value
Age						
<2 years	2 (9.1)	220 (7.2)	3.17 (0.53-19.08)	0.208	1.22 (0.16-9.56)	0.846
2-4 years	7 (31.8)	357 (11.6)	6.84 (1.76-26.58)	0.006	10.42 (2.25-48.36)	0.003
5-14 years	3 (13.6)	1046 (34.1)	1.00	-	1.00	-
15-18 years	10 (45.5)	1448 (47.2)	2.41 (0.66-8.77)	0.183	1.13 (0.27-4.77)	0.863
Type of case-finding						
Passive	15 (68.2)	1478 (48.1)	1.00	-	1.00	-
Active	2 (9.1)	1511 (49.2)	0.13 (0.03-0.57)	0.007	0.13 (0.03-0.66)	0.014
Unknown	5 (22.7)	82 (2.7)	6.01 (2.13-16.93)	0.001	5.41 (1.36-21.44)	0.016
Main localisation of TB						
Lungs	8 (36.4)	1302 (42.4)	1.00	-	1.00	-
CNS	4 (18.2)	49 (1.6)	13.29 (3.87-45.62)	<0.001	5.14 (1.17-22.62)	0.030
Miliary	6 (27.3)	35 (1.1)	27.90 (9.19-84.70)	<0.001	10.25 (2.30-45.67)	0.002
Others	0 (0.0)	1556 (50.7)	n/a	0.987	n/a	0.986
Unknown	4 (18.2)	129 (4.2)	5.05 (1.50-16.99)	0.009	3.51 (0.89-3.89)	0.074
HIV status						
No/unknown	18 (81.8)	3039 (99.0)	1.00	-	1.00	-
HIV positive	4 (18.2)	32 (1.0)	21.10 (6.76-65.86)	<0.001	8.60 (1.57-47.24)	0.013
Previously treated for TB						
No	13 (59.1)	2796 (91.0)	1.00	-	1.00	-
Yes	2 (9.1)	60 (2.0)	7.17 (1.58-32.47)	0.011	10.12 (1.54-66.47)	0.016
Unknown	7 (31.8)	215 (7.0)	7.00 (2.76-17.73)	<0.001	7.89 (2.31-26.92)	0.001
Type of ADR						
No/unknown	19 (86.4)	2900 (94.4)	1.00	-	1.00	-
DILI	2 (9.1)	54 (1.8)	5.65 (1.28-24.87)	0.022	6.50 (1.09-38.71)	0.040
Others	1 (4.5)	117 (3.8)	1.30 (0.17-9.83)	0.796	0.99 (0.11-8.81)	0.992

Hosmer-Lemeshow test, $P=0.976$; area under the ROC curve, 0.96 (95% CI, 0.94-0.99).

Data are presented as number with percentages (%); ADR, adverse drug reaction; aOR, adjusted odds ratio; CI, confidence interval; CNS, central nervous system; cOR, crude odds ratio; DILI, drug-induced liver injury; HIV, human immunodeficiency virus; n/a, not applicable; ROC, receiver operating characteristic.

^aIncluded patients who achieved cure or completed treatment and excluded those who were LTFU or with unknown outcomes.

Table 4. Final model for factors associated with lost to follow-up in children and adolescents treated for TB in the Netherlands

	LTFU (n=160)	Non-LTFU [‡] (n=3071)	cOR (95% CI)	P-value	aOR (95% CI)	P-value
Year of diagnosis [#]	1999 (1995-2003)	2001 (1997-2009)	0.94 (0.92-0.97)	<0.001	0.94 (0.89-0.98)	0.011
Age						
<5 years	24 (15.0)	577 (18.8)	1.28 (0.75-2.18)	0.364	1.47 (0.84-2.59)	0.178
5-14 years	34 (21.3)	1046 (34.1)	1.00	-	1.00	-
15-18 years	102 (63.7)	1448 (47.2)	2.17 (1.46-3.22)	<0.001	1.91 (1.25-2.93)	0.003
Immigrants or asylum seekers						
No	51 (31.9)	1261 (41.1)	1.00	-	1.00	-
Yes, duration <2.5 y	71 (44.4)	1139 (37.1)	1.54 (1.07-2.23)	0.021	1.15 (0.73-1.81)	0.549
Yes, illegal immigrants	8 (5.0)	22 (0.7)	8.99 (3.82-21.17)	<0.001	4.28 (1.60-11.42)	0.004
Yes, duration >2.5 y	17 (10.6)	502 (16.3)	0.84 (0.48-1.46)	0.533	0.59 (0.32-1.10)	0.099
Yes, duration unknown	13 (8.1)	147 (4.8)	2.19 (1.16-4.12)	0.015	1.32 (0.65-2.66)	0.443
Area of living						
Urban ^a	59 (36.9)	854 (27.8)	1.52 (1.09-2.11)	0.014	1.59 (1.10-2.29)	0.014
Suburban ^b	101 (63.1)	2217 (72.2)	1.00	-	1.00	-
Known history of TB contact						
No	135 (84.4)	2090 (68.1)	2.53 (1.64-3.91)	<0.001	1.99 (1.19-3.34)	0.009
Yes	25 (15.6)	981 (31.9)	1.00	-	1.00	-
Drug susceptibility						
Confirmed DS-TB	16 (10.0)	552 (18.0)	1.00	-	1.00	-
Presumed DS-TB	127 (79.4)	2365 (77.0)	1.85 (1.09-3.14)	0.022	1.38 (0.72-2.64)	0.332
Confirmed DR-TB	17 (10.6)	154 (5.0)	3.81 (1.88-7.71)	<0.001	2.31 (1.05-5.10)	0.038
Presence of ADR						
No/unknown	130 (81.3)	2900 (94.4)	1.00	-	1.00	-
Yes, single ADR	19 (11.9)	147 (4.8)	2.88 (1.73-4.80)	<0.001	2.12 (1.18-3.83)	0.012
Yes, multiple ADRs	11 (6.9)	24 (0.8)	10.22 (4.90-21.32)	<0.001	7.84 (3.55-17.33)	<0.001
Treatment interruption >14 days						
No	20 (12.5)	1045 (34.0)	1.00	-	1.00	-
Yes	10 (6.3)	42 (1.4)	12.44 (5.48-28.23)	<0.001	6.93 (2.72-17.63)	<0.001
Unknown	130 (81.3)	1984 (64.6)	3.42 (2.13-5.51)	<0.001	1.03 (0.45-2.35)	0.938
Supervision by PHNs						
No	12 (7.5)	34 (1.1)	1.00	-	1.00	-
Yes	141 (88.1)	2976 (96.9)	0.13 (0.07-0.26)	<0.001	0.14 (0.07-0.29)	<0.001
Unknown	7 (4.4)	61 (2.0)	0.32 (0.12-0.90)	0.031	0.21 (0.07-0.64)	0.006

Hosmer-Lemeshow test, $P=0.745$; area under the ROC curve, 0.75 (95% CI, 0.72-0.79).

Data are presented as number with percentages (%), unless stated otherwise: [#]median with interquartile ranges (IQR); ADR, adverse drug reactions; aOR, adjusted odds ratio; CI, confidence interval; cOR, crude odds ratio; DS-TB, drug-susceptible tuberculosis; DR-TB, drug resistant tuberculosis; LTFU, lost to follow-up; PHNs, public health nurses; ROV, receiver operating characteristics; ROC, receiver operating characteristic.

[‡]Included patients who achieved cure or completed treatment and excluded those who died or with unknown outcomes.

^aThe Hague, Utrecht (stad), Amsterdam and Rotterdam; ^bGroningen, Friesland, Zeeland, Drenthe, Overijssel, Gelderland, Zuid-Holland, Limburg, Utrecht, Noord-Holland, Noord-Brabant, Flevoland or other areas

Table 5. Final model for factors associated with unfavourable outcome in children and adolescents treated for TB in the Netherlands

	Unfavourable [#] (n=325)	Favourable ^β (n=3071)	cOR (95% CI)	P-value	aOR (95% CI)	P-value
Age						
<5 years	61 (16.8)	577 (18.8)	1.38 (0.98-1.96)	0.069	1.58 (1.02-2.46)	0.040
5-14 years	80 (24.6)	1046 (34.1)	1.00	-	1.00	-
15-18 years	184 (56.6)	1448 (47.2)	1.66 (1.26-2.19)	<0.001	1.56 (1.11-2.19)	0.010
Immigrants or asylum seekers						
No	98 (30.2)	1261 (41.1)	1.00	-	1.00	-
Yes, duration <2.5 y	134 (41.2)	1139 (37.1)	1.51 (1.15-1.99)	0.003	1.09 (0.74-1.59)	0.663
Yes, illegal immigrants	17 (5.2)	22 (0.7)	9.94 (5.11-19.34)	<0.001	5.10 (2.15-12.10)	<0.001
Yes, duration >2.5 y	37 (11.4)	502 (16.3)	0.95 (0.64-1.40)	0.791	0.74 (0.45-1.20)	0.222
Yes, duration unknown	39 (12.0)	147 (4.8)	3.41 (2.27-5.14)	<0.001	1.71 (0.99-2.96)	0.054
Known TB contact history						
No	274 (84.3)	2090 (68.1)	2.52 (1.85-3.43)	<0.001	2.00 (1.30-3.07)	0.002
Yes	51 (15.7)	981 (31.9)	1.00	-	1.00	-
Main localisation of TB						
Primary TB infection	30 (9.2)	673 (21.9)	0.54 (0.36-0.82)	0.004	0.85 (0.52-1.41)	0.534
Lungs	107 (32.9)	1302 (42.4)	1.00	-	1.00	-
Respiratory tract	18 (5.5)	388 (12.6)	0.56 (0.34-0.94)	0.029	0.67 (0.39-1.15)	0.146
CNS	7 (2.2)	49 (1.6)	1.74 (0.77-3.93)	0.184	1.52 (0.60-3.87)	0.382
Abdominal	6 (1.8)	51 (1.7)	1.43 (0.60-3.41)	0.418	1.81 (0.72-4.53)	0.207
Osteoarticular	6 (1.8)	67 (2.2)	1.09 (0.46-2.57)	0.844	1.25 (0.51-3.05)	0.629
Other organs	33 (10.2)	377 (12.3)	1.06 (0.71-1.60)	0.761	0.83 (0.53-1.31)	0.427
Miliary	9 (2.8)	35 (1.1)	3.13 (1.46-6.68)	0.003	3.37 (1.42-8.03)	0.006
Unknown	109 (33.5)	129 (4.2)	10.28 (7.45-14.19)	<0.001	3.99 (2.56-6.20)	<0.001
Previously treated for TB						
No	273 (84.0)	2796 (91.0)	1.00	-	1.00	-
Yes	13 (4.0)	60 (2.0)	2.22 (1.20-4.09)	0.011	2.04 (0.98-4.24)	0.057
Unknown	39 (12.0)	215 (7.0)	1.86 (1.29-2.67)	0.001	1.07 (0.67-1.71)	0.765
Presence of ADR						
No/unknown	291 (89.5)	2900 (94.4)	1.00	-	1.00	-
Yes, single ADR	20 (6.2)	147 (4.8)	1.36 (0.84-2.20)	0.216	1.57 (0.89-2.77)	0.120
Yes, multiple ADRs	14 (4.3)	24 (0.8)	5.81 (2.97-11.36)	<0.001	7.54 (3.56-15.99)	<0.001
Treatment interruption >14 days						
No	42 (12.9)	1045 (34.0)	1.00	-	1.00	-
Yes	11 (3.4)	42 (1.4)	6.52 (3.13-13.55)	<0.001	4.90 (2.10-11.42)	<0.001
Unknown	272 (83.7)	1984 (64.6)	3.41 (2.44-4.76)	<0.001	1.58 (1.09-2.92)	0.016
Hospitalised ≥1 week						
No/ <1 week	238 (73.2)	2153 (70.1)	1.00	-	1.00	-
Yes	68 (20.9)	815 (26.5)	0.75 (0.57-1.00)	0.050	0.71 (0.51-1.01)	0.055
Unknown	19 (5.8)	103 (3.4)	1.67 (1.01-2.77)	0.048	0.86 (0.46-1.60)	0.633
Supervised by PHNs						
No	32 (9.8)	34 (1.1)	1.00	-	1.00	-
Yes	192 (59.1)	2976 (96.9)	0.07 (0.04-0.11)	<0.001	0.08 (0.05-0.15)	<0.001
Unknown	101 (31.1)	61 (2.0)	1.76 (0.99-3.14)	0.055	1.01 (0.51-2.00)	0.997

Hosmer-Lemeshow test, $P=0.506$; area under the ROC curve, 0.81 (95% CI, 0.78-0.84).

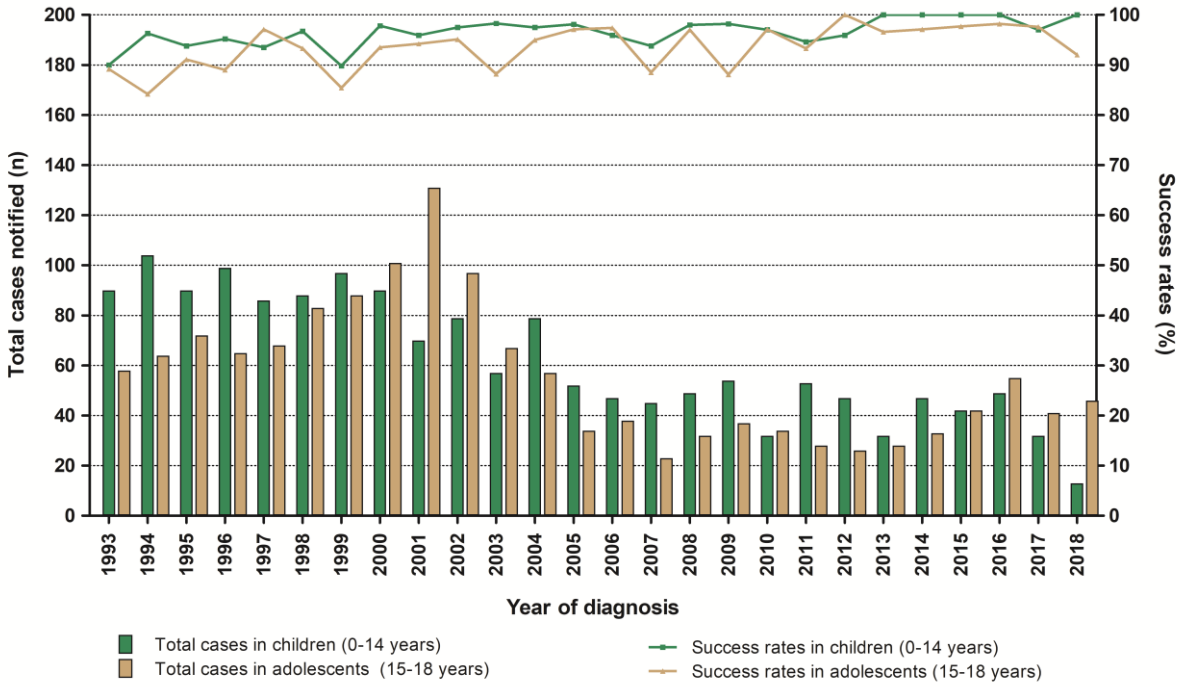
Data are presented as number (n) with percentages, unless stated otherwise: [#]median with interquartile ranges (IQR); ADR, adverse drug reactions; aOR, adjusted odds ratio; CI, confidence interval; CNS, central nervous system; cOR, crude odds ratio; HIV, human immunodeficiency virus; PHNs, public health nurses; ROC, receiver operating characteristic.

^βThe sum of patients who achieved cure or completed treatment.

*The sum of patients who died, were LTFU, or with unknown outcomes

Figure legends:

Figure 1. Notified TB cases and trend of success rates among children and adolescents treated for TB in The Netherlands, 1993-2018



SUPPLEMENTARY FILES:

Supplementary table 1. Operational definitions of the explanatory variables

Variable	Definition
Demographic characteristics	
Children	Patients aged <15 years
Adolescents	Patients aged 15-18 years
WHO Region	Six regions classified by the World Health Organisation (WHO) including African Region, Region of the Americas, South-East Asia Region, European region, Eastern Mediterranean Region, Western Pacific Region
Immigrant	A person who was born outside The Netherlands with a legal residence status other than tourist or refugee.
Non-immigrant	A native Dutch (born in The Netherlands and both parents born in The Netherlands) or a second generation immigrant (born in The Netherlands and have at least one foreign-born parent).
Asylum seeker	A person who has left their home country as a political refugee and is seeking asylum elsewhere.
Urban	Four biggest cities of the Netherlands (The Randstad) including The Hague, Utrecht, Amsterdam and Rotterdam.
Suburban	The province of Groningen, Friesland, Zeeland, Drenthe, Overijssel, Gelderland, Zuid-Holland, Limburg, Utrecht, Noord-Holland, Noord-Brabant, Flevoland or other areas.
TB notification and clinical characteristics	
Active case-finding (ACF)	The systematic screening for active TB cases in a predetermined high-risk group for TB. This included screening for immigrants and refugees, screening for detainees, hospital staff screening, screening for travellers after their journey from TB endemic areas, screening for patients diagnosed with HIV positive, TB-contact investigation, screening for homeless and drug addicts, periodic screening for health care worker or person working with TB risk groups, screening prior to immunosuppressive treatment, X-ray examination for patients with LTBI, and others (screening as a baseline measurement prior to BCG/ travel/ appointment investigation).
Passive case-finding (PCF)	A patient who had experienced TB symptoms (complaints) and came to the healthcare system by their own accord.
Known history of TB contact	A patient who had close contact history with an infectious TB case.
Travel history in TB endemic area >3 month	A patient who had travelled in a country with TB incidence >100 per 100,000 population for more than three months within the past two years.
Pulmonary TB (PTB)	All forms of TB in the lungs, isolated tracheal or bronchus TB, laryngeal TB, and other specified respiratory TB.
Extrapulmonary TB (EPTB)	TB within other locations in the body than the lungs, which may have included isolated EPTB or a combination of PTB and EPTB.
Cavitary TB	Cavitary TB involves the upper lobes of the lung and characterised by the presence of cavities in the lung tissue or enlarged air spaces.
BCG-vaccinated patient	A patient who had a documented medical information of vaccination history or with the presence of a Bacillus Calmette Guerin (BCG) scar
Had TB symptoms	A patient who had symptoms of TB disease prior to treatment. Since 2005, only "cough complaint" was recorded in the database as TB symptoms (applicable only for patients with PTB or PTB+EPTB)
Patient's delay	The number of weeks (at least 1 week) from the onset of TB symptoms and the date of the first contact with health care related to this episode.

Doctor's delay	The number of weeks (at least 1 week) between the first contact with health care for TB episode and the start of TB treatment.
Comorbidity	Comorbidity group was composed by including patients with human immunodeficiency virus (HIV), malignancy, and other diseases (diabetes mellitus, renal insufficiency/ dialysis or organ transplantation).
Bacteriological characteristics	
Smear positive	The specimen from sputum, bronchoalveolar lavage (BAL) or other body materials noted as at least +1 for acid-fast bacilli (AFB+) on microscopy using Ziehl-Neelsen stain.
Species of Mycobacterium	Species of Mycobacterium consists of <i>M. tuberculosis</i> , <i>M. bovis</i> , and other <i>M. tuberculosis</i> complex such as <i>M. africanum</i> , <i>M. microti</i> , <i>M. canetti</i> or unspecified <i>M. tuberculosis</i> complex
Confirmed DS-TB	A patient with a susceptible result of drug-susceptibility testing (DST) for all first-line anti-TB drugs (isoniazid, rifampicin, pyrazinamide and ethambutol).
Presumed DS-TB	A patient treated with first-line anti-TB drugs without sufficient information on DST results
Confirmed DR-TB	A patient with DST results of being resistant to at least one of the first-line TB drugs. Confirmed DR-TB was categorised as mono-resistant, poly-resistance, multidrug-resistant (MDR), or extensively drug-resistant (XDR) TB.
Treatment characteristics	
Retreated patient	A patient who had previously started TB treatment but was discontinued after 1 month or more. It included a patient with treatment after relapse, treatment after failure, treatment after loss to follow-up, and other previously treated cases.
Intermittent dosing	Anti TB-drugs dosing less than once daily during the entire course of treatment or part of the treatment.
Adverse drug reactions (ADRs)	Unwanted and undesirable effects of a medication defined by the treating physician, and demanding an interruption or change of the treatment regimen. ADRs included antituberculosis drug-induced liver injury (DILI), neurological disorders, mental disorders, vision disorders, drug allergy, arthralgia, and others. Any combination of ≥ 2 ADRs were classified as multiple ADRs.
Drug-induced liver injury (DILI)	DILI due to anti-TB drugs was defined as an increased levels of alanine aminotransferase $>3x$ the upper limit of normal (ULN) in the presence of symptoms of hepatotoxicity or $>5x$ the ULN in the absence of symptoms.
Treatment interruption >14 days	A patient who had interrupted treatment to more than 14 days but less than 2 months, either caused by adverse effects or other reasons.
Treatment supervision by public health nurses (PHNs)	Supportive discussions with patients and their family to provide TB education as well as identification of obstacles that influence treatment adherence. The intensity of supervision varies from daily to monthly contacts.
Directly observed therapy (DOT)	Every dose of anti-TB drugs taken under direct observation for a period of time, provided by either PHNs or other selected third parties such as family members or home nursing services

Source: [1,2]

Supplementary table 2. Estimated case-fatality rates stratified by specific sub-population in children and adolescents treated for TB in The Netherlands, 1993-2018

	^a Total, n	Deaths, n	CFR (95% CI)
Total patients	3093	22	0.7 (0.4-1.1)
Stratified by age			
0-4 years	586	9	1.5 (0.7-2.9)
5-14 years	1049	3	0.3 (0.1-0.8)
15-18 years	1458	10	0.7 (0.3-1.3)
Stratified by DST			
Confirmed DS-TB	558	6	1.1 (0.4-2.3)
Presumed DS-TB	2379	14	0.6 (0.3-1.0)
Confirmed DR-TB	156	2	1.3 (0.2-4.6)
Stratified by HIV(+) and age			
HIV(+) aged 0-4 years	4	1	25.0 (0.6-80.6)
HIV(+) aged 5-14 years	10	0	0.0 (0.0-33.6)
HIV(+) aged 15-18 years	23	3	13.0 (2.8-33.6)
Stratified by TB localisation			
Lungs	1310	8	0.6 (0.3-1.2)
CNS	53	4	7.5 (2.1-18.2)
Miliary	41	6	14.6 (5.6-29.2)
Stratified by BCG vaccination and age			
BCG-unvaccinated, aged 0-4 years	405	3	0.7 (0.2-2.1)
BCG-unvaccinated, aged 5-14 years	468	1	0.2 (0.0-1.2)
BCG-unvaccinated, aged 15-18 years	299	1	0.3 (0.0-1.8)

Abbreviations: BCG, Bacillus Calmette-Guerin; CFR, case fatality rate; CI, confidence interval; CNS, central nervous system; DST, drug-susceptibility testing; DS-TB, drug-susceptible tuberculosis; DR-TB, drug-resistant tuberculosis; HIV, human immunodeficiency virus.

^aIncluded patients who were cured, completed treatment or died; and excluded those who were LTFU or with unknown outcomes.

Supplementary table 3. Factors associated with mortality in children and adolescents treated for TB in the Netherlands using univariate logistic regression analysis

	Died (n=22)	Alive ^a (n=3071)	OR (95% CI)	P-value
Demographic characteristics				
Year of diagnosis [#]	2001 (1996-2004)	2001 (1997-2009)	0.95 (0.89-1.01)	0.117
Year of diagnosis				
1993-1998	9 (40.9)	967 (31.5)	1.00	
1999-2003	7 (31.8)	877 (28.6)	0.86 (0.32-2.31)	0.761
2004-2008	4 (18.2)	456 (14.8)	0.94 (0.29-3.08)	0.922
2009-2013	2 (9.1)	371 (12.1)	0.58 (0.12-2.69)	0.486
2014-2018	0 (0.0)	400 (13.0)	n/a	0.993
^a Age				
<2 years	2 (9.1)	220 (7.2)	3.17 (0.53-19.08)	0.208
2-4 years	7 (31.8)	357 (11.6)	6.84 (1.76-26.58)	0.006
5-14 years	3 (13.6)	1046 (34.1)	1.00	-
15-18 years	10 (45.5)	1448 (47.2)	2.41 (0.66-8.77)	0.183
Gender				
Male	12 (54.5)	1690 (55.0)	0.98 (0.42-2.28)	0.981
Female	10 (45.5)	1381 (45.0)	1.00	
Born in The Netherlands				
Yes	7 (31.8)	1252 (40.8)	1.00	
No	15 (68.2)	1795 (58.5)	1.49 (0.61-3.68)	0.381
Unknown	0 (0.0)	24 (0.8)	n/a	0.998
WHO Region of birth				
European	8 (36.4)	1362 (44.4)	1.00	
African	7 (31.8)	565 (18.4)	2.11 (0.76-5.84)	0.151
Eastern Mediterranean	6 (27.3)	879 (28.6)	1.16 (0.40-3.36)	0.782
Other regions	1 (4.5)	241 (7.8)	0.71 (0.09-5.67)	0.744
Unknown	0 (0.0)	24 (0.8)	n/a	0.998
^a Immigrants or asylum seekers				
No	7 (31.8)	1261 (41.1)	1.00	
Yes, duration <2.5 y	5 (22.7)	1139 (37.1)	0.79 (0.25-2.50)	0.698
Yes, illegal immigrants	1 (4.5)	22 (0.7)	8.19 (0.97-69.41)	0.054
Yes, duration >2.5 y	5 (22.7)	502 (16.3)	1.79 (0.57-5.68)	0.320
Yes, duration unknown	4 (18.2)	147 (4.8)	4.90 (1.42-16.94)	0.012
Area of living				
Urban	4 (18.2)	854 (27.8)	1.00	
Suburban	18 (81.8)	2217 (72.2)	1.73 (0.58-5.14)	0.321
TB notification and clinical characteristics				
^a Type of case finding				
Passive	15 (68.2)	1478 (48.1)	1.00	
Active	2 (9.1)	1511 (49.2)	0.13 (0.03-0.57)	0.007
Unknown	5 (22.7)	82 (2.7)	6.01 (2.13-16.93)	0.001
^a Known TB contacts				
No	21 (95.5)	2090 (68.1)	9.86 (1.32-73.38)	0.025
Yes	1 (4.5)	981 (31.9)	1.00	
Travelling in TB endemic area >3 months				
No	21 (95.5)	3044 (99.1)	1.00	
Yes	1 (4.5)	27 (0.9)	5.37 (0.70-41.35)	0.107
^{a,b} Site of TB disease				
PTB	7 (31.8)	1291 (42.0)	1.00	
EPTB	3 (13.6)	1452 (47.3)	0.38 (0.10-1.48)	0.163
PTB + EPTB	12 (54.5)	328 (10.7)	6.75 (2.64-17.27)	<0.001
^{a,b} Main localisation of TB				
Lungs	8 (36.4)	1302 (42.4)	1.00	
CNS	4 (18.2)	49 (1.6)	13.29 (3.87-45.62)	<0.001
Miliary	6 (27.3)	35 (1.1)	27.90 (9.19-84.70)	<0.001

Others	0 (0.0)	1556 (50.7)	n/a	0.987
Unknown	4 (18.2)	129 (4.2)	5.05 (1.50-16.99)	0.009
Cavitary TB				
No	15 (68.2)	2711 (88.3)	1.00	
Yes	3 (13.6)	231 (7.5)	2.35 (0.67-8.17)	0.180
Unknown	4 (18.2)	129 (4.2)	5.60 (1.83-17.12)	0.002
^a BCG-vaccinated				
Yes	6 (27.3)	1163 (37.9)	1.00	
No	5 (22.7)	1167 (38.0)	0.83 (0.25-2.73)	0.760
Unknown	11 (50.0)	741 (24.1)	2.88 (1.06-7.81)	0.038
^a Had TB symptoms				
No	1 (4.5)	930 (30.3)	1.00	
Yes	19 (86.4)	1688 (55.0)	10.47 (1.40-78.32)	0.022
Unknown	2 (9.1)	453 (14.8)	4.10 (0.37-45.40)	0.249
Patient's delay				
No	1 (4.5)	781 (25.4)	1.00	
Yes, >1 week	6 (27.3)	1001 (32.6)	4.68 (0.56-38.96)	0.153
Unknown	15 (68.2)	1289 (42.0)	9.09 (1.20-68.94)	0.033
Doctor's delay				
No	4 (18.2)	577 (18.8)	1.00	
Yes, >1 week	6 (27.3)	930 (30.3)	0.93 (0.26-3.31)	0.912
Unknown	12 (54.5)	1564 (50.9)	1.11 (0.36-3.44)	0.861
Total delay (doctor + patient)				
No	1 (4.5)	103 (3.4)	1.00	
Yes, >1 week	5 (22.7)	952 (31.0)	0.54 (0.06-4.67)	0.577
Unknown	16 (72.7)	2016 (65.6)	0.82 (0.11-6.22)	0.846
^a Comorbidity				
No/unknown	16 (72.7)	3031 (98.7)	1.00	
HIV positive	4 (18.2)	32 (1.0)	23.68 (7.50-74.76)	<0.001
Malignancy ^u	2 (9.1)	4 (0.1)	94.72 (16.18-554.44)	<0.001
Others ^u	0 (0.0)	4 (0.1)	n/a	0.999
Bacteriological characteristics				
Sputum smear microscopy				
Negative	3 (13.6)	480 (15.6)	1.00	
Positive	8 (36.4)	433 (14.1)	2.96 (0.78-11.21)	0.111
Unknown/ not done	11 (50.0)	2158 (70.3)	0.82 (0.23-2.93)	0.755
BAL smear microscopy				
Negative	2 (9.1)	109 (3.5)	1.00	
Positive	5 (22.7)	104 (3.4)	2.62 (0.50-13.80)	0.256
Unknown/ not done	15 (68.2)	2858 (93.1)	0.29 (0.06-1.27)	0.099
Mycobacterial culture				
Negative	1 (4.5)	319 (10.4)	1.00	
Positive	18 (81.8)	1734 (56.5)	3.31 (0.44-24.89)	0.245
Unknown/ not done	3 (13.6)	1018 (33.1)	0.94 (0.10-9.07)	0.957
Species of Mycobacterium				
<i>M. tuberculosis</i>	17 (77.3)	1372 (44.7)	1.00	
Other <i>M. tuberculosis</i> complex	1 (4.5)	79 (2.6)	1.02 (0.13-7.77)	0.984
Unknown	4 (18.2)	1620 (52.8)	0.20 (0.07-0.59)	0.004
Drug susceptibility				
Confirmed DS-TB	6 (27.3)	552 (18.0)	1.00	
Presumed DS-TB	14 (63.6)	2365 (77.0)	0.54 (0.21-1.42)	0.215
Confirmed DR-TB	2 (9.1)	154 (5.0)	1.19 (0.24-5.98)	0.828
Treatment characteristics				
^a Previously treated for TB				
No	13 (59.1)	2796 (91.0)	1.00	
Yes	2 (9.1)	60 (2.0)	7.17 (1.58-32.47)	0.011
Unknown	7 (31.8)	215 (7.0)	7.00 (2.76-17.73)	<0.001
Previously treated for LTBI				
No	3 (13.6)	970 (31.6)	1.00	
Yes	0 (0.0)	78 (2.5)	n/a	0.997

Unknown	19 (86.4)	2023 (65.9)	3.04 (0.90-10.29)	0.074
Drug dosing schedule				
Daily	5 (22.7)	1085 (35.3)	1.00	
Intermittent ^u	0 (0.0)	7 (0.2)	n/a	0.999
Unknown	17 (77.3)	1979 (64.4)	1.86 (0.69-5.07)	0.222
^{a,c} Presence of ADR				
No/unknown	19 (86.4)	2900 (94.4)	1.00	
Yes, single ADR	1 (4.5)	147 (4.8)	1.04 (0.14-7.81)	0.971
Yes, multiple ADRs	2 (9.1)	24 (0.8)	12.72 (2.81-57.66)	0.001
^{a,c} Type of ADR				
No/unknown	19 (86.4)	2900 (94.4)	1.00	
DILI	2 (9.1)	54 (1.8)	5.65 (1.28-24.87)	0.022
Others	1 (4.5)	117 (3.8)	1.30 (0.17-9.83)	0.796
Treatment interruption >14 days				
No	4 (18.2)	1045 (34.0)	1.00	
Yes	0 (0.0)	42 (1.4)	n/a	0.998
Unknown	18 (81.8)	1984 (64.6)	2.37 (0.80-7.02)	0.119
^a Hospitalised ≥1 week				
No/ <1 week	8 (36.4)	2153 (70.1)	1.00	
Yes	10 (45.5)	815 (26.5)	3.30 (1.30-8.40)	0.012
Unknown	4 (18.2)	103 (3.4)	10.45 (3.10-35.27)	<0.001
DOT				
Yes	6 (27.3)	827 (26.9)	1.00	
No	16 (72.7)	2240 (72.9)	0.98 (0.38-2.52)	0.974
Unknown	0 (0.0)	4 (0.1)	n/a	0.999

Data are presented as number (n) with percentages (%), unless stated otherwise: # median with interquartile ranges (IQR).

Abbreviations: ACF, active case finding ; ADR, adverse drug reactions; BAL, bronchoalveolar lavage; BCG, Bacillus Calmette-Guerin; CI, confidence interval; CNS, central nervous system; DILI, drug-induced liver injury; DOT, directly observed therapy; DS-TB, drug-susceptible tuberculosis; DR-TB, drug-resistant tuberculosis; E, ethambutol; EPTB, extra-pulmonary tuberculosis; H, isoniazid; HIV, human immunodeficiency virus; LTBI, latent tuberculosis infection; n/a, not applicable; OR, odds ratio; PCF, passive case finding; PTB, pulmonary tuberculosis; R, rifampicin; Z, pyrazinamide.

^aIncluded patients who achieved cure or completed treatment and excluded those who were LTFU or with unknown outcomes.

^aVariables eligible for inclusion in multivariate analysis.

^{b,c}Due to the likelihood of collinearity, only one of each of these variables was included during the development of the final multivariate model.

^uExcluded from multivariate analysis due to the low number of patients (<20).

Supplementary table 4. Factors associated with lost to follow-up in children and adolescents treated for TB in The Netherlands using univariate logistic regression analysis

	LTFU (n=160)	Non-LTFU [‡] (n=3071)	OR (95% CI)	P-value
Demographic characteristics				
^{a,b} Year of diagnosis [#]	1999 (1995-2003)	2001 (1997-2009)	0.94 (0.92-0.97)	<0.001
^{a,b} Year of diagnosis				
1993-1998	67 (41.9)	967 (31.5)	1.00	
1999-2003	56 (35.0)	877 (28.6)	0.92 (0.64-1.33)	0.662
2004-2008	14 (8.8)	456 (14.8)	0.44 (0.25-0.80)	0.007
2009-2013	14 (8.8)	371 (12.1)	0.54 (0.30-0.98)	0.043
2014-2018	9 (5.6)	400 (13.0)	0.32 (0.16-0.66)	0.002
^a Age				
<5 years	24 (15.0)	577 (18.8)	1.28 (0.75-2.18)	0.364
5-14 years	34 (21.3)	1046 (34.1)	1.00	
15-18 years	102 (63.7)	1448 (47.2)	2.17 (1.46-3.22)	<0.001
^a Gender				
Male	101 (63.1)	1690 (55.0)	1.40 (1.01-1.94)	0.045
Female	59 (36.9)	1381 (45.0)	1.00	
^{a,c} Born in The Netherlands				
Yes	52 (32.5)	1252 (40.8)		
No	108 (67.5)	1795 (58.5)	1.45 (1.03-2.03)	0.032
Unknown	0 (0.0)	24 (0.8)	n/a	0.998
^{a,q} WHO Region of birth				
European	64 (40.0)	1362 (44.4)	1.00	
African	28 (17.5)	565 (18.4)	1.05 (0.67-1.66)	0.819
Eastern Mediterranean	57 (35.6)	879 (28.6)	1.38 (0.96-1.99)	0.085
Americas	0 (0.0)	56 (1.8)	n/a	0.997
South-East Asian	2 (1.3)	79 (2.6)	0.54 (0.13-2.24)	0.395
Western Pacific	9 (5.6)	105 (3.4)	1.82 (0.88-3.77)	0.104
Unknown	0 (0.0)	25 (0.8)	n/a	0.998
^a Immigrants or asylum seekers				
No	51 (31.9)	1261 (41.1)	1.00	
Yes, duration <2.5 y	71 (44.4)	1139 (37.1)	1.54 (1.07-2.23)	0.021
Yes, illegal immigrants	8 (5.0)	22 (0.7)	8.99 (3.82-21.17)	<0.001
Yes, duration >2.5 y	17 (10.6)	502 (16.3)	0.84 (0.48-1.46)	0.533
Yes, duration unknown	13 (8.1)	147 (4.8)	2.19 (1.16-4.12)	0.015
^a Area of living				
Urban	59 (36.9)	854 (27.8)	1.52 (1.09-2.11)	0.014
Suburban	101 (63.1)	2217 (72.2)	1.00	
TB notification and clinical characteristics				
Type of case finding				
Passive	85 (53.1)	1478 (48.1)	1.00	
Active	66 (41.3)	1511 (49.2)	0.76 (0.55-1.06)	0.102
Unknown	9 (5.6)	82 (2.7)	1.91 (0.93-3.93)	0.079
^a Known TB contacts				
No	135 (84.4)	2090 (68.1)	2.53 (1.64-3.91)	<0.001
Yes	25 (15.6)	981 (31.9)	1.00	
Travelling in TB endemic area >3 months				
No	158 (98.8)	3044 (99.1)	1.00	
Yes	2 (1.3)	27 (0.9)	1.43 (0.34-6.05)	0.630
Site of TB disease				
PTB	67 (41.9)	1291 (42.0)	1.00	
EPTB	71 (44.4)	1452 (47.3)	0.94 (0.67-1.33)	0.733
PTB + EPTB	22 (13.8)	328 (10.7)	1.29 (0.79-2.12)	0.311
^a Main localisation of TB				
Primary TB infection	21 (13.1)	673 (21.9)	0.56 (0.34-0.93)	0.023
Lungs	72 (45.0)	1302 (42.4)	1.00	

Respiratory tract	16 (10.0)	388 (12.6)	0.75 (0.43-1.30)	0.299
CNS	1 (0.6)	49 (1.6)	0.37 (0.05-2.71)	0.327
Abdominal	4 (2.5)	51 (1.7)	1.42 (0.50-4.03)	0.512
Osteoarticular	5 (3.1)	67 (2.2)	1.35 (0.53-3.45)	0.532
Other organs	24 (15.0)	377 (12.3)	1.15 (0.71-1.85)	0.562
Miliary	2 (1.3)	35 (1.1)	1.03 (0.24-4.38)	0.965
Unknown	15 (9.4)	129 (4.2)	2.10 (1.17-3.77)	0.013
Cavitary TB				
No	132 (82.5)	2711 (88.3)	1.00	
Yes	13 (8.1)	231 (7.5)	1.16 (0.64-2.07)	0.628
Unknown	15 (9.4)	129 (4.2)	2.39 (1.36-4.19)	0.002
BCG-vaccinated				
Yes	58 (36.3)	1163 (37.9)	1.00	
No	52 (32.5)	1167 (38.0)	0.89 (0.61-1.31)	0.564
Unknown	50 (31.3)	741 (24.1)	1.35 (0.92-2.00)	0.128
Had TB symptoms				
No	49 (30.6)	930 (30.3)	1.00	
Yes	93 (58.1)	1688 (55.0)	1.05 (0.73-1.49)	0.805
Unknown	18 (11.3)	453 (14.8)	0.75 (0.43-1.31)	0.316
Patient's delay				
No	46 (28.7)	781 (25.4)	1.00	
Yes, 1-4 weeks	25 (15.6)	608 (19.8)	0.70 (0.42-1.15)	0.158
Yes, 5-8 weeks	12 (7.5)	168 (5.5)	1.21 (0.63-2.34)	0.565
Yes, >8 weeks	11 (6.9)	225 (7.3)	0.83 (0.42-1.63)	0.588
Unknown	66 (41.3)	1289 (42.0)	0.87 (0.59-1.28)	0.478
Doctor's delay				
No	33 (20.6)	577 (18.8)	1.00	
Yes, 1-4 weeks	33 (20.6)	556 (18.1)	1.04 (0.63-1.70)	0.884
Yes, 5-8 weeks	10 (6.3)	137 (4.5)	1.28 (0.61-2.65)	0.513
Yes, >8 weeks	12 (7.5)	237 (7.7)	0.88 (0.45-1.74)	0.725
Unknown	72 (45.0)	1564 (50.9)	0.80 (0.53-1.23)	0.315
Total delay (doctor + patient)				
No	6 (3.8)	103 (3.4)	1.00	
Yes, 1-4 weeks	23 (14.4)	332 (10.8)	1.19 (0.47-3.00)	0.714
Yes, 5-8 weeks	9 (5.6)	206 (6.7)	0.75 (0.26-2.16)	0.595
Yes, >8 weeks	24 (15.0)	414 (13.5)	0.99 (0.40-2.50)	0.992
Unknown	98 (61.3)	2016 (65.6)	0.83 (0.36-1.95)	0.676
Comorbidity				
No/unknown	158 (98.8)	3031 (98.7)	1.00	
HIV positive	0 (0.0)	32 (1.0)	n.a	0.998
Malignancy	1 (0.6)	4 (0.1)	4.80 (0.53-43.16)	0.162
Others	1 (0.6)	4 (0.1)	4.80 (0.53-43.16)	0.162
Bacteriological characteristics				
Sputum smear microscopy				
Negative	25 (15.6)	480 (15.6)	1.00	
Positive	18 (11.3)	433 (14.1)	0.80 (0.43-1.48)	0.476
Unknown/ not done	117 (73.1)	2158 (70.3)	1.04 (0.67-1.62)	0.859
BAL smear microscopy				
Negative	6 (3.8)	109 (3.5)	1.00	
Positive	3 (1.9)	104 (3.4)	0.52 (0.13-2.15)	0.370
Unknown/ not done	151 (94.4)	2858 (93.1)	0.96 (0.41-2.22)	0.924
Mycobacterial culture				
Negative	13 (8.1)	319 (10.4)	1.00	
Positive	104 (65.0)	1734 (56.5)	1.47 (0.82-2.65)	0.198
Unknown/ not done	43 (26.9)	1018 (33.1)	1.04 (0.55-1.95)	0.912
Species of Mycobacterium				
<i>M. tuberculosis</i>	77 (48.1)	1372 (44.7)	1.00	
Other <i>M. tuberculosis</i> complex	4 (2.5)	79 (2.6)	0.90 (0.32-2.53)	0.845
Unknown	79 (49.4)	1620 (52.8)	0.87 (0.63-0.20)	0.392
^a Drug susceptibility				

Confirmed DS-TB	16 (10.0)	552 (18.0)	1.00	
Presumed DS-TB	127 (79.4)	2365 (77.0)	1.85 (1.09-3.14)	0.022
Confirmed DR-TB	17 (10.6)	154 (5.0)	3.81 (1.88-7.71)	<0.001
Treatment characteristics				
Previously treated for TB				
No	140 (87.5)	2796 (91.0)	1.00	
Yes	6 (3.8)	60 (2.0)	2.00 (0.85-4.70)	0.113
Unknown	14 (8.8)	215 (7.0)	1.30 (0.74-2.29)	0.363
Previously treated for LTBI				
No	29 (18.1)	970 (31.6)	1.00	
Yes	3 (1.9)	78 (2.5)	1.29 (0.38-4.32)	0.683
Unknown	128 (80.0)	2023 (65.9)	2.12 (1.40-3.19)	<0.001
^a Drug dosing schedule				
Daily	30 (18.8)	1085 (35.3)	1.00	
Intermittent [‡]	3 (1.9)	7 (0.2)	15.50 (3.82-62.87)	<0.001
Unknown	127 (79.4)	1979 (64.4)	2.32 (1.55-3.48)	<0.001
^{a,d} Presence of ADR				
No/unknown	130 (81.3)	2900 (94.4)	1.00	
Yes, single ADR	19 (11.9)	147 (4.8)	2.88 (1.73-4.80)	<0.001
Yes, multiple ADRs	11 (6.9)	24 (0.8)	10.22 (4.90-21.32)	<0.001
^{a,d} Type of ADR				
No/unknown	130 (81.3)	2900 (94.4)	1.00	
DILI	7 (4.4)	54 (1.8)	2.89 (1.29-6.48)	0.010
Others	23 (14.4)	117 (3.8)	4.38 (2.71-7.09)	<0.001
^a Treatment interruption >14 days				
No	20 (12.5)	1045 (34.0)	1.00	
Yes	10 (6.3)	42 (1.4)	12.44 (5.48-28.23)	<0.001
Unknown	130 (81.3)	1984 (64.6)	3.42 (2.13-5.51)	<0.001
Hospitalised ≥1 week				
No/ <1 week	106 (66.3)	2153 (70.1)	1.00	
Yes	42 (26.3)	815 (26.5)	1.05 (0.73-1.51)	0.807
Unknown	12 (7.5)	103 (3.4)	2.37 (1.26-4.44)	0.007
^a Supervised by PHNs				
No	12 (7.5)	34 (1.1)	1.00	
Yes	141 (88.1)	2976 (96.9)	0.13 (0.07-0.26)	<0.001
Unknown	7 (4.4)	61 (2.0)	0.32 (0.12-0.90)	0.031
^a DOT				
Yes	32 (20.0)	827 (26.9)	1.00	
No	127 (79.4)	2240 (72.9)	1.46 (0.99-2.18)	0.059
Unknown	1 (0.6)	4 (0.1)	6.46 (0.70-59.46)	0.099

Data are presented as number (n) with percentages, unless stated otherwise: # median with interquartile ranges (IQR).

Abbreviations: ADR, adverse drug reactions; BAL, bronchoalveolar lavage; BCG, Bacillus Calmette Guerin; CI, confidence interval; CNS, central nervous system; DILI, drug-induced liver injury; DOT, directly observed therapy; DS-TB, drug-susceptible tuberculosis; DR-TB, drug-resistant tuberculosis; E, ethambutol; EPTB, extra-pulmonary tuberculosis; H, isoniazid; HIV, human immunodeficiency virus; LTFU, lost to follow-up; LTBI, latent tuberculosis infection; n/a, not applicable; OR, odds ratio; PHNs, public health nurses; PTB, pulmonary tuberculosis; R, rifampicin; Z, pyrazinamide.

[‡]Included patients who achieved cure or completed treatment and excluded those who died or with unknown outcomes.

^aVariable eligible for inclusion in multivariate analysis.

^{b,c,d}Due to the likelihood of collinearity, only one of each of these variables was included during the development of the final multivariate model.

[‡]Excluded from multivariate analysis due to the low number of patients (<20).

Supplementary table 5. Factors associated with unfavourable outcome in children and adolescents treated for TB in The Netherlands using univariate logistic regression analysis

	Unfavourable [‡] (n=325)	Favourable [§] (n=3071)	OR (95% CI)	P-value
Demographic characteristics				
^{a,b} Year of diagnosis [#]	2000 (1995-2003)	2001 (1997-2009)	0.95 (0.93-0.96)	<0.001
^{a,b} Year of diagnosis				
1993-1998	125 (38.5)	967 (31.5)	1.00	
1999-2003	128 (39.4)	877 (28.6)	1.13 (0.87-1.47)	0.365
2004-2008	29 (8.9)	456 (14.8)	0.49 (0.32-0.75)	0.001
2009-2013	27 (8.3)	371 (12.1)	0.56 (0.36-0.87)	0.009
2014-2018	16 (4.9)	400 (13.0)	0.31 (0.18-0.53)	<0.001
^a Age				
<5 years	61 (16.8)	577 (18.8)	1.38 (0.98-1.96)	0.069
5-14 years	80 (24.6)	1046 (34.1)	1.00	
15-18 years	184 (56.6)	1448 (47.2)	1.66 (1.26-2.19)	<0.001
^a Gender				
Male	203 (62.5)	1690 (55.0)	1.36 (1.07-1.72)	0.011
Female	122 (37.5)	1381 (45.0)	1.00	
^{a,c} Born in The Netherlands				
Yes	98 (30.2)	1252 (40.8)	1.00	
No	222 (68.3)	1795 (58.5)	1.58 (1.23-2.03)	<0.001
Unknown	5 (1.5)	24 (0.8)	2.66 (0.99-7.13)	0.051
^{a,q} WHO Region of birth				
European	118 (36.3)	1362 (44.4)	1.00	
African	62 (19.1)	565 (18.4)	1.27 (0.92-1.75)	0.151
Eastern Mediterranean	117 (36.0)	879 (28.6)	1.54 (1.17-2.01)	0.002
Americas	1 (0.3)	56 (1.8)	0.21 (0.03-1.50)	0.119
South-East Asian	6 (1.8)	79 (2.6)	0.88 (0.37-2.05)	0.762
Western Pacific	16 (4.9)	105 (3.4)	1.76 (1.01-3.07)	0.048
Unknown	5 (1.5)	25 (0.8)	2.31 (0.87-6.14)	0.094
^a Immigrants or asylum seekers				
No	98 (30.2)	1261 (41.1)	1.00	
Yes, duration <2.5 y	134 (41.2)	1139 (37.1)	1.51 (1.15-1.99)	0.003
Yes, illegal immigrants	17 (5.2)	22 (0.7)	9.94 (5.11-19.34)	<0.001
Yes, duration >2.5 y	37 (11.4)	502 (16.3)	0.95 (0.64-1.40)	0.791
Yes, duration unknown	39 (12.0)	147 (4.8)	3.41 (2.27-5.14)	<0.001
Area of living				
Urban	85 (26.2)	854 (27.8)	0.92 (0.71-1.19)	0.526
Suburban	240 (73.8)	2217 (72.2)	1.00	
TB notification and clinical characteristics				
^a Type of case finding				
Passive	170 (52.3)	1478 (48.1)	1.00	
Active	136 (41.8)	1511 (49.2)	0.78 (0.62-0.99)	0.042
Unknown	19 (5.8)	82 (2.7)	2.01 (1.19-3.40)	0.009
^a Known TB contacts				
No	274 (84.3)	2090 (68.1)	2.52 (1.85-3.43)	<0.001
Yes	51 (15.7)	981 (31.9)	1.00	
Travelling in TB endemic area >3 months				
No	321 (98.8)	3044 (99.1)	1.00	
Yes	4 (1.2)	27 (0.9)	1.40 (0.49-4.04)	0.528
^{a,d} Site of TB disease				
PTB	163 (50.2)	1291 (42.0)	1.00	
EPTB	118 (36.3)	1452 (47.3)	0.64 (0.50-0.82)	0.001
PTB + EPTB	44 (13.5)	328 (10.7)	1.06 (0.74-1.51)	0.737
^{a,d} Main localisation of TB				
Primary TB infection	30 (9.2)	673 (21.9)	0.54 (0.36-0.82)	0.004
Lungs	107 (32.9)	1302 (42.4)	1.00	

Respiratory tract	18 (5.5)	388 (12.6)	0.56 (0.34-0.94)	0.029
CNS	7 (2.2)	49 (1.6)	1.74 (0.77-3.93)	0.184
Abdominal	6 (1.8)	51 (1.7)	1.43 (0.60-3.41)	0.418
Osteoarticular	6 (1.8)	67 (2.2)	1.09 (0.46-2.57)	0.844
Other organs	33 (10.2)	377 (12.3)	1.06 (0.71-1.60)	0.761
Miliary	9 (2.8)	35 (1.1)	3.13 (1.46-6.68)	0.003
Unknown	109 (33.5)	129 (4.2)	10.28 (7.45-14.19)	<0.001
Cavitary TB				
No	197 (60.6)	2711 (88.3)	1.00	
Yes	19 (5.8)	231 (7.5)	1.13 (0.69-1.85)	0.620
Unknown	109 (33.5)	129 (4.2)	11.63 (8.67-15.59)	<0.001
BCG-vaccinated				
Yes	117 (36.0)	1163 (37.9)	1.00	
No	107 (32.9)	1167 (38.0)	0.91 (0.69-1.20)	0.508
Unknown	101 (31.1)	741 (24.1)	1.35 (1.02-1.80)	0.035
Had TB symptoms				
No	93 (28.6)	930 (30.3)	1.00	
Yes	199 (61.2)	1688 (55.0)	1.18 (0.91-1.53)	0.213
Unknown	33 (10.2)	453 (14.8)	0.73 (0.48-1.10)	0.132
Patient's delay				
No	88 (27.1)	781 (25.4)	1.00	
Yes, 1-4 weeks	54 (16.6)	608 (19.8)	0.79 (0.55-1.12)	0.189
Yes, 5-8 weeks	24 (7.4)	168 (5.5)	1.27 (0.78-2.05)	0.334
Yes, >8 weeks	24 (7.4)	225 (7.3)	0.95 (0.59-1.52)	0.821
Unknown	135 (41.5)	1289 (42.0)	0.93 (0.70-1.23)	0.612
Doctor's delay				
No	56 (17.2)	577 (18.8)	1.00	
Yes, 1-4 weeks	72 (22.2)	556 (18.1)	1.33 (0.92-1.93)	0.125
Yes, 5-8 weeks	19 (5.8)	137 (4.5)	1.43 (0.82-2.48)	0.206
Yes, >8 weeks	21 (6.5)	237 (7.7)	0.91 (0.54-1.54)	0.733
Unknown	157 (48.3)	1564 (50.9)	1.03 (0.75-1.42)	0.836
Total delay (doctor + patient)				
No	9 (2.8)	103 (3.4)	1.00	
Yes, 1-4 weeks	40 (12.3)	332 (10.8)	1.38 (0.65-2.94)	0.405
Yes, 5-8 weeks	20 (6.2)	206 (6.7)	1.11 (0.49-2.53)	0.802
Yes, >8 weeks	49 (15.1)	414 (13.5)	1.35 (0.64-2.85)	0.423
Unknown	207 (63.7)	2016 (65.6)	1.17 (0.59-2.36)	0.650
^a Comorbidity				
No/unknown	314 (96.6)	3031 (98.7)	1.00	
HIV positive	7 (2.2)	32 (1.0)	2.11 (0.92-4.82)	0.076
Malignancy ^μ	3 (0.9)	4 (0.1)	7.24 (1.61-32.49)	0.010
Others	1 (0.3)	4 (0.1)	2.41 (0.27-21.66)	0.431
Bacteriological characteristics				
Sputum smear microscopy				
Negative	58 (17.8)	480 (15.6)	1.00	
Positive	46 (14.2)	433 (14.1)	0.88 (0.58-1.32)	0.536
Unknown/ not done	221 (68.0)	2158 (70.3)	0.85 (0.62-1.15)	0.289
BAL smear microscopy				
Negative	16 (4.9)	109 (3.5)	1.00	
Positive	15 (4.6)	104 (3.4)	0.98 (0.46-2.09)	0.964
Unknown/ not done	294 (90.5)	2858 (93.1)	0.70 (0.41-1.20)	0.195
^{a,e} Mycobacterial culture				
Negative	21 (6.5)	319 (10.4)	1.00	
Positive	187 (57.5)	1734 (56.5)	1.64 (1.03-2.61)	0.038
Unknown/ not done	117 (36.0)	1018 (33.1)	1.75 (1.08-2.82)	0.023
^{a,e} Species of Mycobacterium				
<i>M. tuberculosis</i>	151 (46.5)	1372 (44.7)	1.00	
<i>M. bovis</i>	5 (1.5)	18 (0.6)	2.52 (0.92-6.89)	0.071
Other <i>M. tuberculosis</i> complex	3 (0.9)	61 (2.0)	0.45 (0.14-1.44)	0.178
Unknown	166 (51.1)	1620 (52.8)	0.93 (0.74-1.17)	0.546

^a Drug susceptibility				
Confirmed DS-TB	39 (12.0)	552 (18.0)	1.00	
Presumed DS-TB	260 (80.0)	2365 (77.0)	1.56 (1.10-2.21)	0.013
Confirmed DR-TB	26 (8.0)	154 (5.0)	2.39 (1.41-4.05)	0.001
Treatment characteristics				
^a Previously treated for TB				
No	273 (84.0)	2796 (91.0)	1.00	
Yes	13 (4.0)	60 (2.0)	2.22 (1.20-4.09)	0.011
Unknown	39 (12.0)	215 (7.0)	1.86 (1.29-2.67)	0.001
Previously treated for LTBI				
No	54 (16.6)	970 (31.6)	1.00	
Yes	4 (1.2)	78 (2.5)	0.92 (0.32-2.61)	0.877
Unknown	267 (82.2)	2023 (65.9)	2.37 (1.75-3.21)	<0.001
^a Drug dosing schedule				
Daily	56 (17.2)	1085 (35.3)	1.00	
Intermittent ^u	3 (0.9)	7 (0.2)	8.30 (2.09-32.97)	0.003
Unknown	266 (81.8)	1979 (64.4)	2.60 (1.93-3.51)	<0.001
^{a,f} Presence of ADR				
No/unknown	291 (89.5)	2900 (94.4)	1.00	
Yes, single ADR	20 (6.2)	147 (4.8)	1.36 (0.84-2.20)	0.216
Yes, multiple ADRs	14 (4.3)	24 (0.8)	5.81 (2.97-11.36)	<0.001
^{a,f} Type of ADR				
No/unknown	291 (89.5)	2900 (94.4)	1.00	
DILI	9 (2.8)	54 (1.8)	1.66 (0.81-3.40)	0.165
Others	25 (7.7)	117 (3.8)	2.13 (1.36-3.33)	0.001
^a Treatment interruption >14 days				
No	42 (12.9)	1045 (34.0)	1.00	
Yes	11 (3.4)	42 (1.4)	6.52 (3.13-13.55)	<0.001
Unknown	272 (83.7)	1984 (64.6)	3.41 (2.44-4.76)	<0.001
^a Hospitalised ≥1 week				
No/ <1 week	238 (73.2)	2153 (70.1)	1.00	
Yes	68 (20.9)	815 (26.5)	0.75 (0.57-1.00)	0.050
Unknown	19 (5.8)	103 (3.4)	1.67 (1.01-2.77)	0.048
^a Supervised by PHNs				
No	32 (9.8)	34 (1.1)	1.00	
Yes	192 (59.1)	2976 (96.9)	0.07 (0.04-0.11)	<0.001
Unknown	101 (31.1)	61 (2.0)	1.76 (0.99-3.14)	0.055
^a DOT				
Yes	50 (15.4)	827 (26.9)	1.00	
No	271 (83.4)	2240 (72.9)	2.00 (1.46-2.73)	<0.001
Unknown	4 (1.2)	4 (0.1)	16.54 (4.02-68.09)	<0.001

Data are presented as number (n) with percentages, unless stated otherwise: #median with interquartile ranges (IQR).

Abbreviations: ADR, adverse drug reactions; BAL, bronchoalveolar lavage; BCG, Bacillus Calmette Guerin; CI, confidence interval; CNS, central nervous system; DILI, drug-induced liver injury; DOT, directly observed therapy; DS-TB, drug-susceptible tuberculosis; DR-TB, drug-resistant tuberculosis; E, ethambutol; EPTB, extra-pulmonary tuberculosis; H, isoniazid; HIV, human immunodeficiency virus; LTBI, latent tuberculosis infection; OR, odds ratio; PHNs, public health nurses; PTB, pulmonary tuberculosis; R, rifampicin; Z, pyrazinamide.

^βThe sum of patients who achieved cure or completed treatment.

[¥]The sum of patients who died, were LTFU, or with unknown outcomes.

^aVariable eligible for inclusion in multivariate analysis.

^{b,c,d,e,f}Due to the likelihood of collinearity, only one of each of these variables was included during the development of the final multivariate model.

^uExcluded from multivariate analysis due to the low number of patients (<20).

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