

## SUPPLEMENTARY FILES:

Supplementary table S1. Operational definitions of the explanatory variables

Variable	Definition
<b>Demographic characteristics</b>	
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): The Hague, Utrecht, Amsterdam and Rotterdam.
Suburban	Provinces of the Netherlands: Groningen, Friesland, Zeeland, Drenthe, Overijssel, Gelderland, Zuid-Holland, Limburg, Utrecht, Noord-Holland, Noord-Brabant, Flevoland or other areas.
<b>TB notification and clinical characteristics</b>	
Active case-finding	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 (e.g. screening as a baseline measurement prior to BCG/ travel/ appointment investigation).
Passive case-finding	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 months	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, including mediastinal lymphadenopathy, 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 vaccination	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).
<b>Bacteriological characteristics</b>	
Smear positive	The specimen from sputum, bronchoalveolar lavage 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 monoresistant, polyresistant, multidrug-resistant (MDR)-, or extensively drug-resistant (XDR)-TB.
<b>Treatment characteristics</b>	
Retreated patient	A patient who had previously started TB treatment but was discontinued after 1 month or more. This 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 $\geq 2$ 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.
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 by PHNs varies from daily to monthly contacts.
Directly observed therapy	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 S2. Estimated case-fatality rates stratified by specific sub-population in children and adolescents treated for TB in The Netherlands, 1993-2018

	<sup>a</sup> 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.

<sup>a</sup>Included patients who were cured, completed treatment or died; and excluded those who were LTFU or with unknown outcomes.

Supplementary table S3. Factors associated with mortality in children and adolescents treated for TB in the Netherlands using univariate logistic regression analysis

	Died (n=22)	Alive <sup>a</sup> (n=3071)	OR (95% CI)	P-value
<b>Demographic characteristics</b>				
Year of diagnosis <sup>#</sup>	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
<sup>a</sup> 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
<sup>a</sup> 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
<b>TB notification and clinical characteristics</b>				
<sup>a</sup> 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
<sup>a</sup> 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
<sup>a,b</sup> 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
<sup>a,b</sup> 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
<sup>a</sup> 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
<sup>a</sup> 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
<sup>a</sup> 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 <sup>u</sup>	2 (9.1)	4 (0.1)	94.72 (16.18-554.44)	<0.001
Others <sup>u</sup>	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				
<sup>a</sup> 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 <sup>u</sup>	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
<sup>a,c</sup> 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
<sup>a,c</sup> 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
<sup>a</sup> 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.

<sup>a</sup>Included patients who achieved cure or completed treatment and excluded those who were LTFU or with unknown outcomes.

<sup>a</sup>Variables eligible for inclusion in multivariate analysis.

<sup>b,c</sup>Due to the likelihood of collinearity, only one of each of these variables was included during the development of the final multivariate model.

<sup>u</sup>Excluded from multivariate analysis due to the low number of patients (<20).

Supplementary table S4. 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 <sup>£</sup> (n=3071)	OR (95% CI)	P-value
<b>Demographic characteristics</b>				
<sup>a,b</sup> Year of diagnosis <sup>#</sup>	1999 (1995-2003)	2001 (1997-2009)	0.94 (0.92-0.97)	<0.001
<sup>a,b</sup> 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
<sup>a</sup> 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
<sup>a</sup> 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	
<sup>a,c</sup> 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
<sup>a,c</sup> 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
<sup>a</sup> 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
<sup>a</sup> 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	
<b>TB notification and clinical characteristics</b>				
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
<sup>a</sup> 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
<sup>a</sup> 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
<b>Bacteriological characteristics</b>				
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
<sup>a</sup> 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
<b>Treatment characteristics</b>				
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
<sup>a</sup> Drug dosing schedule				
Daily	30 (18.8)	1085 (35.3)	1.00	
Intermittent <sup>‡</sup>	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
<sup>a,d</sup> 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
<sup>a,d</sup> 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
<sup>a</sup> 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
<sup>a</sup> 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
<sup>a</sup> 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.

<sup>‡</sup>Included patients who achieved cure or completed treatment and excluded those who died or with unknown outcomes.

<sup>a</sup>Variable eligible for inclusion in multivariate analysis.

<sup>b,c,d</sup>Due to the likelihood of collinearity, only one of each of these variables was included during the development of the final multivariate model.

<sup>‡</sup>Excluded from multivariate analysis due to the low number of patients (<20).

Supplementary table S5. Factors associated with unfavourable outcome in children and adolescents treated for TB in The Netherlands using univariate logistic regression analysis

	Unfavourable <sup>‡</sup> (n=325)	Favourable <sup>§</sup> (n=3071)	OR (95% CI)	P-value
<b>Demographic characteristics</b>				
<sup>a,b</sup> Year of diagnosis <sup>#</sup>	2000 (1995-2003)	2001 (1997-2009)	0.95 (0.93-0.96)	<0.001
<sup>a,b</sup> 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
<sup>a</sup> 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
<sup>a</sup> 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	
<sup>a,c</sup> 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
<sup>a,c</sup> 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
<sup>a</sup> 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	
<b>TB notification and clinical characteristics</b>				
<sup>a</sup> 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
<sup>a</sup> 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
<sup>a,d</sup> 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
<sup>a,d</sup> 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
<sup>a</sup> 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 <sup>μ</sup>	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
<b>Bacteriological characteristics</b>				
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
<sup>a,e</sup> 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
<sup>a,e</sup> 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

<sup>a</sup> 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				
<sup>a</sup> 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
<sup>a</sup> Drug dosing schedule				
Daily	56 (17.2)	1085 (35.3)	1.00	
Intermittent <sup>u</sup>	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
<sup>a,f</sup> 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
<sup>a,f</sup> 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
<sup>a</sup> 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
<sup>a</sup> 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
<sup>a</sup> 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
<sup>a</sup> 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.

<sup>β</sup>The sum of patients who achieved cure or completed treatment.

<sup>\*</sup>The sum of patients who died, were LTFU, or with unknown outcomes.

<sup>a</sup>Variable eligible for inclusion in multivariate analysis.

<sup>b,c,d,e,f</sup>Due to the likelihood of collinearity, only one of each of these variables was included during the development of the final multivariate model.

<sup>u</sup>Excluded from multivariate analysis due to the low number of patients (<20).

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