

Supplementary material:

Towards elimination of childhood and adolescent tuberculosis in the Netherlands: an epidemiological time-series analysis of national routine surveillance data.

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Supplementary methods

Data sources

The NTR is a nationwide database managed by the Dutch National Institute for Public Health and the Environment (RIVM) containing information from continuous surveillance on the occurrence of LTBI and TB disease of all patients in the Netherlands. Since 1993, detailed information on patient demographics, diagnosis (clinical and bacteriology), comorbidities, treatment characteristics and treatment outcomes were collected through an electronic system and registered to the NTR by the Municipal Public Health Services (MPHSs). This registration would be cross-checked and verified at individual level for completeness and consistency through an interactive process with the MPHSs by the KNCV Tuberculosis Foundation (before 2012) or by the RIVM (since 2012).

Data analysis

Patient selection

Secondary study outcomes included severe forms of TB, prolonged patient and health system delays, mycobacterial culture results, and MDR-TB. First, severe forms of TB consisted of cavitary PTB, CNS TB and miliary TB. Considering the different nature of disease progression and clinical presentation between cavitary TB (severe form of PTB) versus CNS TB or miliary TB (severe forms of EPTB or combined PTB/EPTB), and also to prevent overlapping of patients included in these two groups, data analyses were performed separately in patients with PTB and in patients with EPTB or combined PTB/EPTB. Patients with cavitary TB were compared to other PTB cases without the presence of pulmonary cavitation; this definition excluded patients with EPTB or combined PTB/EPTB, and those with missing information on disease localisations. Patients with CNS or miliary TB were compared to other EPTB or combined PTB/EPTB cases; this definition excluded patients with PTB only, those with pulmonary cavitation, and with missing information on disease

localisations. Second, patient and health system delays were only applicable for patients with PTB or combined PTB/EPTB who experienced TB symptoms (persistent cough). These symptomatic patients with PTB or combined PTB/EPTB who had prolonged patient delay >4 weeks were compared to those who had delays ≤ 4 weeks; this definition excluded patients with EPTB only, and those with unknown information on patient delay. Similarly, symptomatic PTB cases or combined PTB/EPTB cases who had prolonged health system delay >4 weeks were compared to those who had delays ≤ 4 weeks; this definition excluded patients with EPTB only, and those with unknown information on health system delay. Third, patients who were culture-positive for *M. tuberculosis* complex were compared to those who were culture-negative; this definition excluded patients with unknown information on mycobacterial culture results. Lastly, patients with confirmed MDR-TB or extensively drug-resistant TB were compared to those with confirmed drug-susceptible TB; this definition excluded patients with mono/poly-resistant TB, and those with missing information on DST results.

Statistical analysis

Associations of patient characteristics with severe forms of TB, prolonged patient and health system delays, positive mycobacterial cultures, and MDR-TB were evaluated using univariate and multivariate logistic regression analyses. All variables in the univariate analysis showing a trend towards association with each of the study outcomes as mentioned above, and with a minimum number of 15 patients in any particular subgroup of predictors, were eligible for inclusion in multivariate analysis. These variables were selected using backward deletion, and the final multivariate models retained all variables with a p-value <0.1. To evaluate the goodness of fit and performance of the final models, Hosmer-Lemeshow test and the area under the receiver operating characteristic curve were used, respectively. Crude and adjusted odds ratios (ORs) along with 95% CI were used to estimate the association between explanatory variables and study outcomes. Statistical significance was accepted at $p < 0.05$, whereas p-values of 0.05-0.1 were considered trends. Data were analysed using SPSS Statistics (version 25.0; IBM, NY, USA).

Table S1. Operational definitions of all variables used in this study [1].

Variable	Definition
Demographic characteristics	
Children	Patients aged 0-14 years [2].
Adolescents	Patients aged 15-19 years.
Dutch-born patients	Patients born in the Netherlands, consisted of either native Dutch (born in The Netherlands and both parents born in The Netherlands) or second-generation immigrants (born in The Netherlands and have at least one foreign-born parent)
Foreign-born patients	Patients born outside the Netherlands (first-generation immigrants). These included patients who were detected within the first 6 months after arrival in the Netherlands (period covered by entry screening), during 6-29 months after arrival (follow-up screening period), and at a later stage after follow-up screening.
Immigrant	A person with legal residence status other than tourist/ refugee/ asylum seeker.
Asylum seeker	A person who seeks safety from persecution or serious harm, and awaits a decision on the application for refugee status.
Urban areas	Four biggest cities (municipalities) of the Netherlands: The Hague, Utrecht, Amsterdam and Rotterdam.
Suburban areas	Twelve provinces of the Netherlands: Groningen, Friesland, Zeeland, Drenthe, Overijssel, Gelderland, Zuid-Holland, Limburg, Utrecht, Noord-Holland, Noord-Brabant, Flevoland or other areas.
TB background and clinical characteristics	
Active case-finding	Systematic screening for active TB in predetermined high-risk groups, including screening for immigrants and asylum seekers, 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 investigations, screening for homeless and drug addicts, periodic screening for health care workers or persons 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 with TB symptoms (especially, persistent cough) presenting to the healthcare system by their own accord.
Known history of TB contact	A patient who had contact history with an infectious TB case.
Travel history from TB-endemic areas	A patient who had travelled for more than three months within the past two years in a country with TB incidence >50/100,000 population (until 2013) or >100/100,000 population (from 2014 onwards).
Pulmonary TB (PTB)	TB in the lungs, isolated tracheal or bronchus TB, laryngeal TB, and other specified respiratory TB.
Extrapulmonary TB (EPTB)	TB in locations other than the lungs, including mediastinal/hilar lymphadenopathy.
Combined PTB/EPTB	A combination of both PTB and EPTB, including miliary TB.
Severe forms of TB	Severe forms of TB included cavitary PTB, TB of central nervous system (CNS; including meningitis TB), and miliary TB.
Cavitary TB	The presence of pulmonary cavitation in the lung tissue or enlarged air spaces, involving the upper lobes of the lung (applicable for patients with PTB or combined PTB/EPTB).
Previous BCG vaccination	A patient who had a documented medical information of vaccination

	history or with a presence of a Bacillus Calmette-Guerin (BCG) scar.
TB symptoms	A patient who had symptoms of TB disease prior to treatment. Since 2005, only “persistent cough” was recorded in the NTR database as TB symptoms (applicable for patients with PTB or combined PTB/EPTB).
Patient delay	The time (in weeks) from initial onset of TB symptoms to the patient's first consultation with a healthcare provider (applicable for patients with symptomatic PTB or combined PTB/EPTB).
Health system delay	The time (in weeks) from the patient's first consultation with a healthcare provider to the initiation of TB treatment (applicable for patients with symptomatic PTB or combined PTB/EPTB).
Bacteriological characteristics	
Smear positive	The specimen from sputum, bronchoalveolar lavage or other body materials noted as at least +1 for acid-fast bacilli on microscopy using Ziehl-Neelsen or Auramine stains.
Species of Mycobacterium	Species of Mycobacterium consisted of <i>M. tuberculosis</i> and other <i>M. tuberculosis</i> complex such as <i>M. bovis</i> , <i>M. africanum</i> , <i>M. microti</i> , <i>M. canetti</i> or unspecified <i>M. tuberculosis</i> complex
Drug-susceptible TB	Susceptible results of drug-susceptibility testing to first-line TB drugs (at least to isoniazid and rifampicin)
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	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 multidrug-resistant TB.

References:

1. National Institute for Public Health and the Environment (RIVM). Osiris-NTR Tuberculose ziekte: Vragenlijst en handleiding 2017 [Osiris-NTR Tuberculosis Disease: Questionnaire and Manual 2017]. Available from: <https://www.rivm.nl/documenten/osiris-ntr-ziekte-vragenlijst-2017>.
2. World Health Organization (WHO). Guidance for national tuberculosis programmes on the management of tuberculosis in children (2nd ed). World Health Organization; 2014.

Table S2. Final model for factors associated with positive mycobacterial cultures in children and adolescents with tuberculosis (TB) in the Netherlands.

	Culture-positive	Culture-negative	cOR (95% CI)	p-value	aOR (95% CI)	p-value
Cases, n	2313	375				
Year of diagnosis, median (IQR)	2001 (1997-2008)	2006 (2002-2013)	0.91 (0.90; 0.93)	<0.0001	0.89 (0.87; 0.91)	<0.0001
Age						
<2 years	87 (3.8)	19 (5.1)	1.53 (0.85; 2.75)	0.1581	1.06 (0.52; 2.14)	0.8729
2-4 years	106 (4.6)	41 (10.9)	0.86 (0.53; 1.39)	0.5419	0.61 (0.34; 1.08)	0.0914
5-9 years	156 (6.7)	52 (13.9)	1.00	-	1.00	-
10-14 years	348 (15.0)	79 (21.1)	1.47 (0.99; 2.18)	0.0583	1.02 (0.63; 1.64)	0.9394
15-19 years	1616 (69.9)	184 (49.1)	2.93 (2.06; 4.15)	<0.0001	1.93 (1.25; 2.98)	0.0029
Origin						
Dutch-born	650 (28.1)	153 (40.8)	1.00	-	1.00	-
Foreign-born	1663 (71.9)	222 (59.2)	1.76 (1.41; 2.21)	<0.0001	1.40 (1.05; 1.88)	0.0222
Presence of TB symptoms						
No	437 (18.9)	140 (37.3)	1.00	-	1.00	-
Yes	1597 (69.0)	143 (38.1)	3.58 (2.77; 4.62)	<0.0001	1.79 (1.29; 2.45)	0.0005
Unknown	279 (12.1)	92 (24.5)	0.97 (0.72; 1.31)	0.8518	3.22 (2.00; 5.17)	<0.0001
Type of case-finding						
Active	708 (30.6)	220 (58.7)	1.00	-	1.00	-
Passive	1556 (67.3)	142 (37.9)	3.40 (2.71; 4.28)	<0.0001	4.86 (3.54; 6.66)	<0.0001
Unknown	49 (2.1)	13 (3.5)	1.17 (0.62; 2.20)	0.6229	1.31 (0.63; 2.73)	0.4647
Site of TB						
Pulmonary TB	1260 (54.5)	115 (30.7)	3.14 (2.46; 4.01)	<0.0001	8.42 (5.90; 12.02)	<0.0001
EPTB	740 (32.0)	212 (56.5)	1.00	-	1.00	-
Pulmonary TB + EPTB	313 (13.5)	48 (12.8)	1.87 (1.33; 2.62)	0.0003	4.13 (2.65; 6.43)	<0.0001

Data are presented as n (%), unless otherwise stated. cOR: crude odds ratio; aOR: adjusted odds ratio; CI: confidence intervals; EPTB: extrapulmonary tuberculosis; n/a: not applicable. Hosmer-Lemeshow test: $p=0.947$. Area under the receiver operating characteristic curve (95% CI): 0.82 (0.80-0.84). Patients with unknown history of TB contact and who received Bacillus Calmette-Guerin vaccination had a significantly increased odds of being culture-positive for *Mycobacterium tuberculosis* complex in univariate analysis but did not found significant in multivariate analysis.

Table S3. Final model for factors associated with multidrug-resistant tuberculosis (MDR-TB) in children and adolescents in the Netherlands.

	MDR-TB	DS-TB	cOR (95% CI)	P-value	aOR (95% CI)	P-value
Cases, n	38	763				
Year of diagnosis*	2003 (1998-2012)	2010 (2006-2015)	0.90 (0.85; 0.94)	<0.0001	0.90 (0.86; 0.95)	<0.0001
Origin						
Dutch-born	5 (13.2)	213 (28.0)	1.00	-	1.00	-
African-born	28 (73.7)	431 (56.6)	2.77 (1.05; 7.27)	0.0388	2.70 (0.99; 7.32)	0.0513
Asian-born	4 (10.5)	75 (9.8)	2.27 (0.59; 8.68)	0.2303	1.50 (0.37; 6.05)	0.5665
Others	1 (2.6)	43 (5.6)	0.99 (0.11; 8.69)	0.9933	0.56 (0.06; 5.29)	0.6112
Type of case-finding						
Active	16 (42.1)	190 (24.9)	2.36 (1.20; 4.65)	0.0129	2.26 (1.11; 4.61)	0.0252
Passive	20 (52.6)	561 (73.6)	1.00	-	1.00	-
Unknown	2 (5.3)	11 (1.4)	5.10 (1.06; 24.54)	0.0421	4.59 (0.84; 24.99)	0.0778
Previously treated for TB						
No	31 (81.6)	692 (90.8)	1.00	-	1.00	-
Yes	5 (13.2)	14 (1.8)	7.97 (2.70; 23.54)	0.0002	8.54 (2.55; 28.55)	0.0005
Unknown	2 (5.3)	56 (7.3)	0.80 (0.19; 3.42)	0.7603	0.61 (0.14; 2.71)	0.5155

Data are presented as n (%), unless otherwise stated: *median (interquartile ranges). MDR-TB: multidrug-resistant tuberculosis (resistant to at least both isoniazid and rifampicin); DS-TB: drug-susceptible tuberculosis (fully susceptible to all first-line anti-TB drugs including isoniazid, rifampicin, pyrazinamide and ethambutol); cOR: crude odds ratio; aOR: adjusted odds ratio; CI: confidence intervals; n/a: not applicable. Hosmer-Lemeshow test: p=0.228. Area under the receiver operating characteristic curve (95% CI): 0.76 (0.67; 0.85). In univariate analysis, there were no other factors associated with MDR-TB.

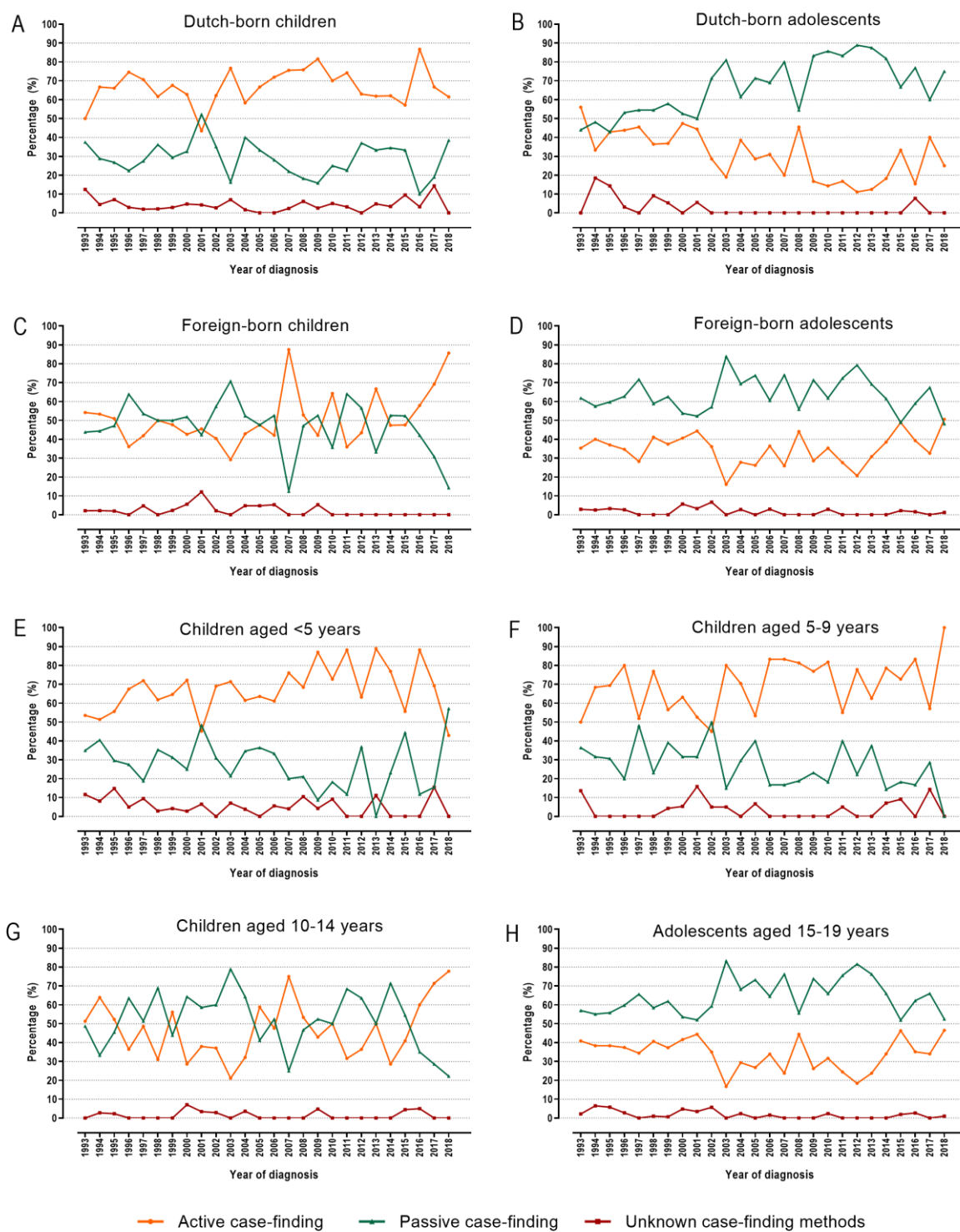


Figure S1. Methods of case-finding in children and adolescents with TB in the Netherlands, stratified by country of birth and age. Active case-finding was defined as a systematic screening for TB cases in predetermined risk groups, whereas passive case-finding was defined as patients with TB symptoms coming to the healthcare system by their own accord.



Figure S2. Notification rate estimates of tuberculosis (TB) in children and adolescents in the Netherlands, stratified by geographical area of residence. TB notification rate estimates from 1993-2018 are presented per 100,000 person-years.

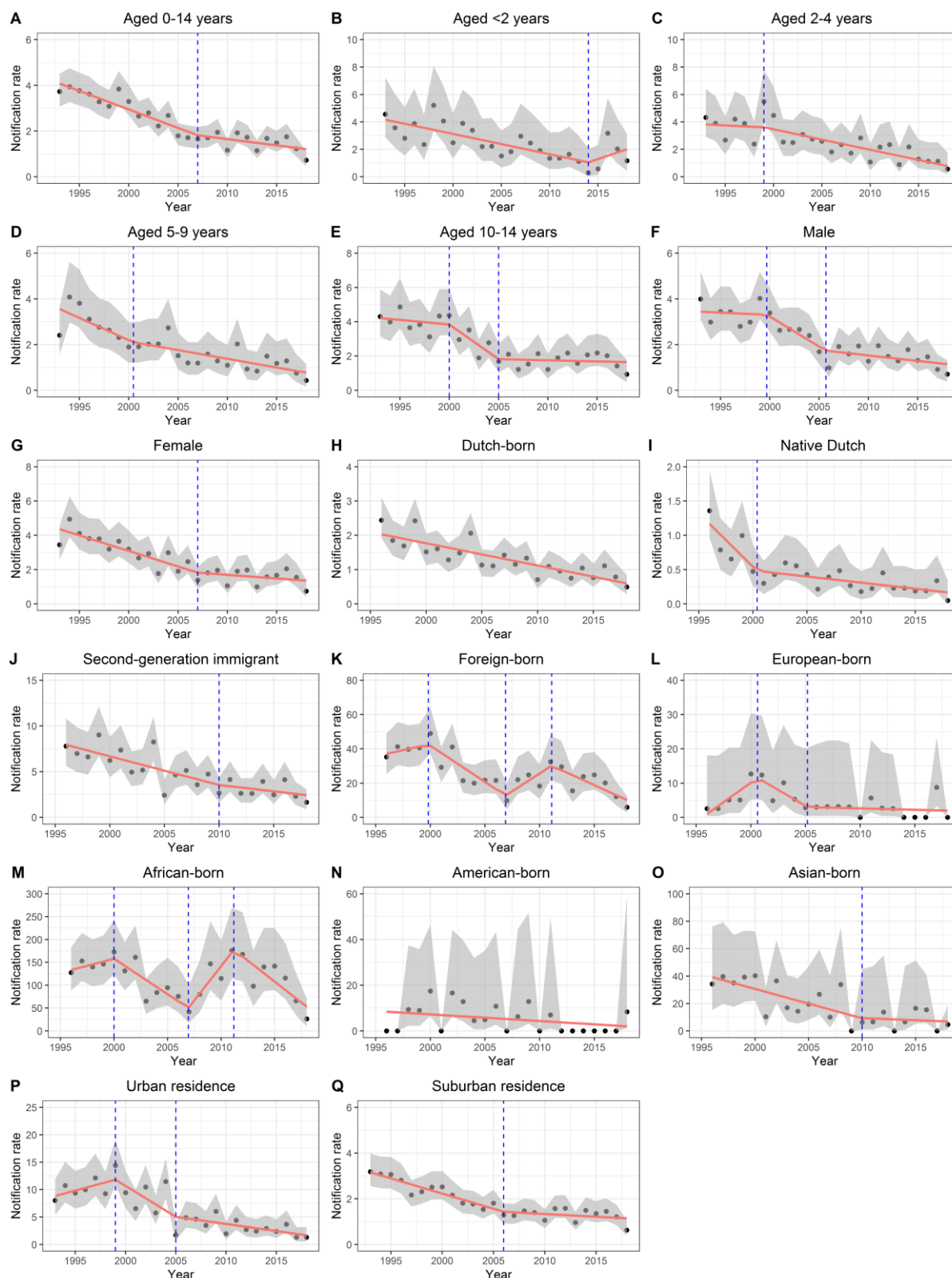


Figure S3. Tuberculosis (TB) notification rate estimates and trends of notification rates in children aged <15 years stratified by different demographic groups, during 1993-2018 (A-G, P and Q) or during 1996-2018 (H-O). TB notification rates with 95% confidence intervals (black points with grey areas) were estimated using Poisson regression models offset with log population size, and are presented per 100,000 person-years. Confidence intervals of notification rates were not calculated for certain years with zero number of TB cases. Trends in notification rates (red lines) were estimated using segmented linear regression analysis.

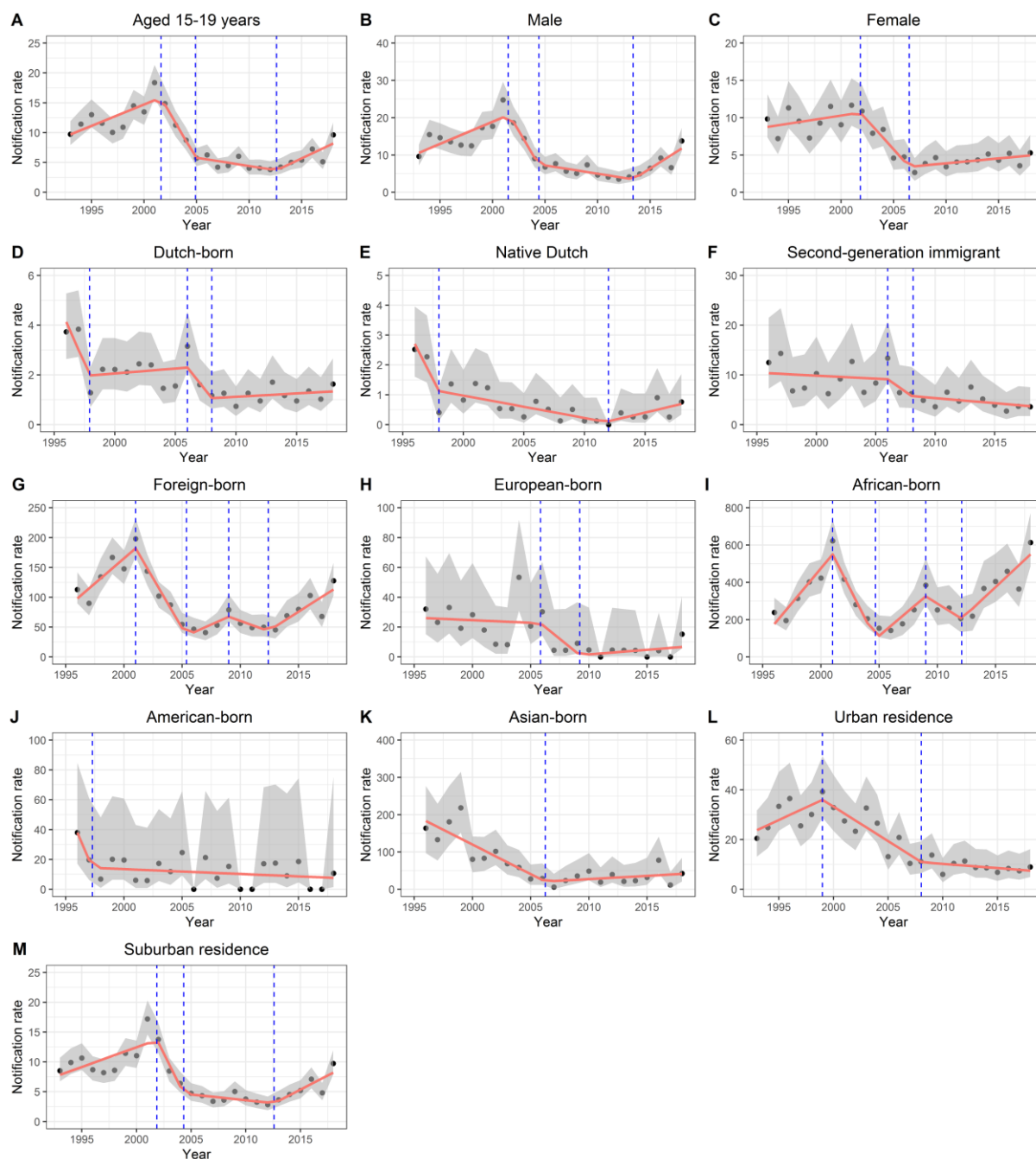


Figure S4. Tuberculosis (TB) notification rate estimates and trends of notification rates in adolescents aged 15-19 years stratified by different demographic groups, during 1993-2018 (A-C, L and M) or 1996-2018 (D-K). TB notification rates with 95% confidence intervals (black points with grey areas) were estimated using Poisson regression models offset with log population size, and are presented per 100,000 person-years. Confidence intervals of notification rates were not calculated for certain years with zero number of TB cases. Trends in notification rates (red lines) were estimated using segmented linear regression analysis.

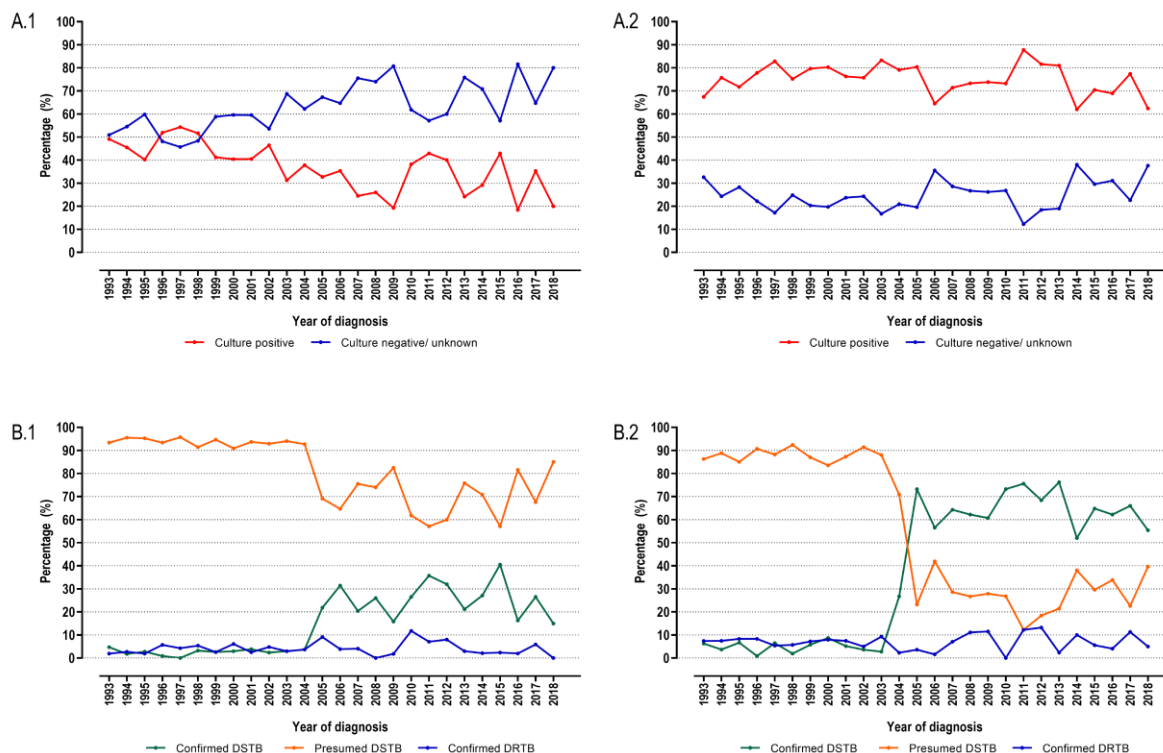


Figure S5. Mycobacterial culture and drug-susceptibility testing results in children aged <15 years and in adolescents aged 15-19 years with tuberculosis (TB) during 1993-2018 in the Netherlands. (A.1) Mycobacterial culture results in children. (A.2) Mycobacterial culture results in adolescents. (B.1) Drug-susceptibility testing results in children. (B.2) Drug-susceptibility testing results in adolescents. Confirmed DSTB (drug-susceptible TB): patients with susceptible results of drug-susceptibility testing to at least isoniazid and rifampicin; presumed DSTB: patients treated with first-line anti-TB drugs without sufficient information on drug-susceptibility testing; confirmed DRTB (drug-resistant TB): resistance to at least one first-line anti-TB drug.