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

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During 1993–2018, TB notification in children in the Netherlands declined steadily, but there was an increase of TB in foreign-born adolescents. Enhancing active case-finding through contact investigation and entry screening is needed to optimise TB control. https://bit.ly/36AjNhm

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ABSTRACT

Background: Tuberculosis (TB) in children and adolescents is a sentinel event for ongoing transmission. In the Netherlands, epidemiological characteristics of childhood and adolescent TB have not been fully evaluated. Therefore, we aimed to assess TB epidemiology within this population to provide guidance for TB elimination.

Methods: A retrospective time-series analysis using national surveillance data from 1993–2018 was performed in children (aged <15 years) and adolescents (aged 15–19 years) with TB. Poisson regression models offset with log-population size were used to estimate notification rates and rate ratios. Trends in notification rates were estimated using average annual percentage changes (AAPC) based on the segmented linear regression analysis.

Results: Among 3899 children and adolescents with TB notified during 1993–2018, 2418 (62%) were foreign-born (725 (41.3%) out of 1755 children and 1693 (78.9%) out of 2144 adolescents). The overall notification rate in children was 2.3 per 100 000 person-years, declining steadily during the study period (AAPC −10.9%, 95% CI −12.6–−9.1). In adolescents, the overall notification rate was 8.4 per 100 000 person-years, strongly increasing during 1993–2001 and 2012–2018. Compared to Dutch-born children and adolescents, substantially higher notification rates were observed among African-born children and adolescents (116.8 and 316.6 per 100 000 person-years, respectively). Additionally, an increasing trend was observed in African-born adolescents (AAPC 18.5%, 95% CI 11.9–25.5). Among the foreign-born population, those from countries in the horn of Africa contributed most to the TB caseload.

Conclusion: TB notification rate among children was low and constantly declining across different demographic groups. However, heterogeneities were shown in adolescents, with an increasing trend in the foreign-born, particularly those from Africa.

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Introduction

Tuberculosis (TB) remains a major global health challenge, with an estimated 1.1 million new cases and 205 000 deaths in children aged <15 years in 2018 [1]. The risk of death is highest in children aged <5 years and among those with HIV co-infection not receiving antiretroviral therapy [2–5]. While TB is considered treatable and curable, management of childhood TB faces significant challenges, due to the lack of sensitive diagnostic tools, the lack of adaptable treatment approaches for both TB infection and TB disease, and poor access to child-friendly drug formulations with proven efficacy and limited toxicity [6–8]. Similarly, even with a significant burden of the disease [9], adolescents have been neglected in TB surveillance due to the fragmented approach of grouping all persons aged <15 years as children and those aged ⩾15 years as adults, leaving little specific knowledge on TB epidemiology, prevention and management for this population [10–12].

In high-income countries, TB is still a concern, and a major cause of morbidity and mortality among migrant populations originating from high TB incidence countries [13]. Importantly, TB in children is a sentinel event reflecting recent transmission of *Mycobacterium tuberculosis* from adults [12]. In the Netherlands, the burden and trends in childhood TB notification rates during 1993–2012 by migration status (*i.e.* first-generation immigrant, native Dutch and second-generation immigrant) have been reported [14]. However, a complete picture of epidemiological characteristics in other demographic groups of children is lacking. Furthermore, adolescents with TB have not been considered as a specific group in any epidemiological study in the Netherlands, providing a gap in understanding the TB burden within this population. Our study aimed to assess the epidemiology of childhood and adolescent TB including national estimates of notification rates, rate ratios and trends in notification rates, stratified by several demographic groups such as age, sex, country of birth, migration status and geographical area of residence. Our secondary aims were to describe clinical and bacteriological characteristics, to optimise screening for TB in high-risk groups and provide guidance for TB elimination.

Methods

Data sources and study population

This was a retrospective observational time-series analysis using data obtained from the Netherlands Tuberculosis Register (NTR; more details are given in the supplementary material). All children and adolescents aged <20 years with TB notified to the NTR between January 1993 and December 2018 were included in this study; patients with missing information for country of birth were excluded. TB diagnosis follows the criteria set by the World Health Organization (WHO) European Region [15], including TB confirmed by culture identifying *M. tuberculosis* complex, and those clinically diagnosed with TB (without bacteriological confirmation).

Data collection

Anonymised data of TB cases were obtained from the NTR on November 13, 2019, consisting of demographics (year of diagnosis, age, sex, origin, migration status and geographical area of residence), TB background and clinical characteristics (type of case-finding, history of TB contact, travel history in TB-endemic areas, disease sites, previous treatment of TB infection or disease, bacille Calmette–Guérin (BCG) vaccination, TB symptoms (especially persistent cough), HIV status, patient delay and health system delay) and bacteriological characteristics (smear microscopy, mycobacterial culture and drug-susceptibility testing (DST)).

Definitions

Individuals aged 0–14 years at diagnosis were defined as children following the WHO recommendations for reporting childhood TB [16], and those aged 15–19 years were defined as adolescents. Foreign-born

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patients (first-generation immigrants) included those detected within the first 6 months after arrival in the country (period covered by entry screening), during 6–29 months after arrival (follow-up screening period) and at a later stage after follow-up screening. Dutch-born patients consisted of either native Dutch (born in the Netherlands with both parents born in the Netherlands) or second-generation immigrants (born in the Netherlands and have at least one foreign-born parent). Active case finding (ACF) was defined as the systematic screening for TB disease in predetermined high-risk groups, while passive case-finding (PCF) was defined as patients self-presented to the healthcare system because of TB symptoms. TB in the lungs, isolated tracheal or bronchus TB, laryngeal TB and other specified respiratory TB, were classified as pulmonary TB (PTB). TB in locations other than the lungs, including mediastinal/hilar lymphadenopathy, were classified as extrapulmonary TB (EPTB). Severe forms of TB included cavitary PTB, TB of the central nervous system (CNS; including meningitis) and miliary TB. Patient delay was defined as the time between initial onset of TB symptoms and the patient's first consultation with a healthcare provider. Health system delay was defined as the time from the patient's first consultation with a healthcare provider to treatment initiation. A cut-off of >4 weeks was used to define either prolonged patient delay or health system delay [17]. Both delays were applicable for patients with symptomatic PTB or combined PTB/EPTB. Since 2005, only "persistent cough" was registered in the NTR as TB symptom; other signs and symptoms of TB were not registered. DST results of resistance to at least isoniazid and rifampicin were defined as multidrug-resistant (MDR)-TB. Until 2005, DST results were not systematically registered in the NTR, and were only registered if resistance against isoniazid or rifampicin was detected. Definitions of other variables are presented in supplementary table S1.

Data analysis

Notification rates and rate ratios along with 95% confidence intervals, were estimated using Poisson regression models, offset with log population size. Overall and stratum-specific notification rate estimates from 1993–2018 were reported per 100 000 person-years, unless otherwise stated. Total annual population in different demographic groups from 1993–2018 (refer to the situation on January 1 of the year of observation), were derived from the Central Agency for Statistics (Statistics Netherlands (CBS) https://opendata.cbs.nl/statline/#/CBS/en/). Given that population numbers based on migration status and country of birth have only been available since 1996, notification rate estimates in these particular groups were calculated from 1996–2018. Trends in notification rates were estimated using average annual percent changes (AAPC) based on the segmented linear regression analysis [18]. Data were analysed using R-3.6.0 for Windows; additionally, the R package "segmented" was used for segmented analysis (www.CRAN.R-project.org/package=segmented). Associations of patient characteristics with severe forms of TB, prolonged patient and health system delays, mycobacterial culture results and MDR-TB were evaluated using univariate and multivariate logistic regression analyses. For these secondary outcomes, details are provided in the supplementary material.

Ethics

As this was a retrospective study using anonymous routinely collected data, ethics clearance and individual patient written informed consent were not required under Dutch law (https://wetten.overheid.nl/BWBR0007021/2006-02-01). Research approval was obtained from the research committee of the NTR. All TB prevention and control activities, including those for high-risk groups, follow the guidelines set by the Dutch Government and the WHO European Region [15, 19].

Results

Demographic characteristics

Among 31 376 TB cases notified to the NTR during 1993–2018, 3931 (12.5%) were children and adolescents. After excluding 32 patients with missing information for country of birth, 3899 records (1755 (45.0%) children and 2144 (55%) adolescents) were eligible for analysis. Foreign-born patients accounted for 2418 (62%) of the 3899 study population (725 (41.3%) out of 1755 children and 1693 (78.9%) out of 2144 adolescents). Of these, 692 (28.6%), 787 (32.5%) and 707 (29.2%) had lived in the Netherlands for <6 months, 6–29 months and ⩾30 months at the time of diagnosis, respectively. Annual number of TB cases during 1993–2018 in Dutch-born children were relatively higher compared to foreign-born children (figure 1ai). In contrast, the annual number of TB cases in foreign-born adolescents constantly exceeded Dutch-born adolescents over the whole period (figure 1aii). TB cases in Dutch-born children were mostly detected through ACF (685 (66.5%) out of 1030), while the proportions of TB cases detected through ACF *versus* PCF in foreign-born children were approximately equal (345 (47.6%) *versus* 362 (49.9%) out of 725, respectively). In adolescents, most of the patients were detected through PCF: 286 (63.4%) of 451 Dutch-born and 1046 (61.8%) of 1693 foreign-born (table 1). Furthermore, children aged <5 years and aged 5–10 years were more likely to be detected through ACF, irrespective of their country of birth (supplementary figure S1).

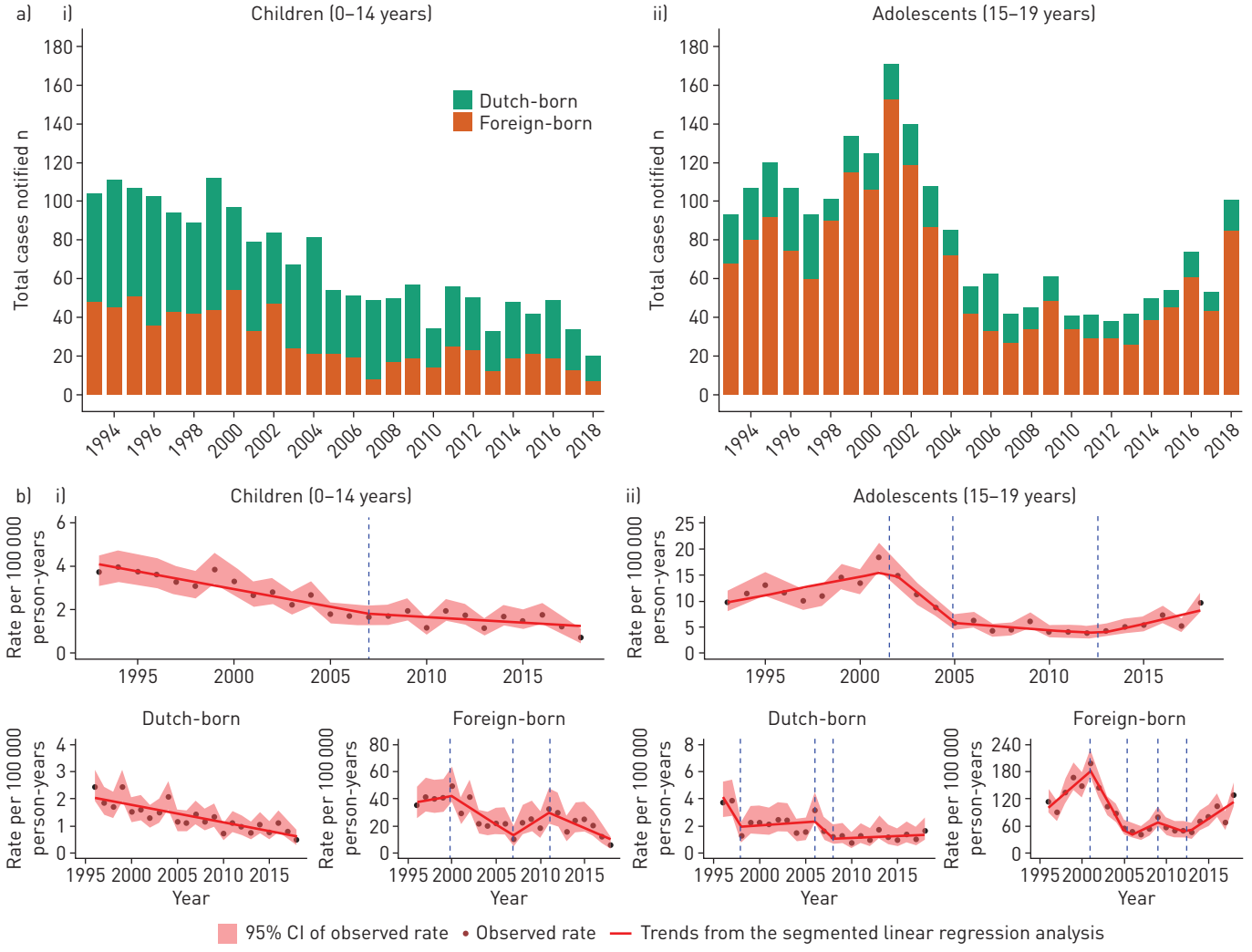

FIGURE 1 Number of annual tuberculosis (TB) cases and notification rate estimates in children and adolescents in the Netherlands. a) Number of annual TB cases in Dutch- and foreign-born i) children and ii) adolescents from 1993–2018; b) TB notification rate estimates per 100 000 person-years in i) children and ii) adolescents from 1996–2018, stratified by Dutch- and foreign-born.

Notification rate estimates and trends

During 1993–2018, the overall TB notification rate in the total population aged 0–19 years was 3.8 per 100 000 person-years (95% CI 3.3–4.5). In children, the overall rate was 2.3 per 100 000 person-years. The rate in foreign-born children was 26.3 per 100 000 person-years, 20.0 times higher than in Dutch-born (95% CI 11.9–33.0). Among subgroups of children, the highest rate occurred in African-born children (116.8 per 100 000 person-years), whereas native Dutch children had the lowest rate (0.4 per 100 000 person-years). In adolescents, the overall rate was 8.4 per 100 000 person-years, 3.6 times higher than in children (95% CI 2.6–5.0). With an estimated notification of 93.7 per 100 000 person-years, foreign-born adolescents had 53.4 times higher rate compared to Dutch-born adolescents (95% CI 31.7–95.7). Among adolescent subgroups, the highest rate occurred in African-born adolescents (316.6 per 100 000 person-years), while the lowest rate occurred in native Dutch adolescents (0.7 per 100 000 person-years). Compared to the overall years from 1993–2018, notification rates during 2014–2018 were lower in all demographic groups, except for African-born adolescents: 447.3 per 100 000 person-years (table 2).

Among the foreign-born population, those from countries in the horn of Africa contributed most to the TB caseload. Overall, notification rates among Somali-born children and adolescents during 1996–2018 were 300.4 and 778.5 per 100 000 person-years, respectively. During 2014–2018, Somalian and Eritrean birth accounted for 56 (70.9%) out of 79 TB cases among foreign-born children, and 201 (73.6%) out of 273 TB cases among foreign-born adolescents (figure 2a). Detailed results for notification rates based on 30 selected countries of birth are presented in figure 2b. Stratified by area of residence, Amsterdam, Rotterdam and The Hague accounted for the highest overall notification rates in both children and adolescents, particularly during the earlier period from 1993 to around 2005 (supplementary figure S2).

TABLE 1 Demographic and clinical characteristics of children and adolescents with tuberculosis (TB) in the Netherlands, 1993–2018

	Children (0–14 years)			Adolescents (15–19 years)		
	Dutch-born	Foreign-born	p-value	Dutch-born	Foreign-born	p-value
Cases n	1030	725		451	1693	
Year of diagnosis						
1993–1998	343 (33.3)	265 (36.6)	0.1588	156 (34.6)	465 (27.5)	0.0030
1999–2003	237 (23.0)	202 (27.9)	0.0208	98 (21.7)	580 (34.3)	<0.0001
2004–2008	199 (19.3)	86 (11.9)	<0.0001	82 (18.2)	208 (12.3)	0.0011
2009–2013	137 (13.3)	93 (12.8)	0.7723	56 (12.4)	167 (9.9)	0.1146
2014–2018	114 (11.1)	79 (10.9)	0.9100	59 (13.1)	273 (16.1)	0.1124
Age						
<2 years	207 (20.1)	39 (5.4)	<0.0001			
2–4 years	296 (28.7)	91 (12.6)	<0.0001			
5–9 years	290 (28.2)	181 (25.0)	<0.0001			
10–14 years	237 (23.0)	414 (57.1)	0.3632			
Sex						
Male	522 (50.7)	334 (46.1)	0.0571	267 (59.2)	1061 (62.7)	0.1777
Female	508 (49.3)	391 (53.9)	0.0571	184 (40.8)	632 (37.3)	0.1777
Residential area						
Urban[#]	392 (38.1)	152 (21.0)	<0.0001	177 (39.2)	353 (20.9)	<0.0001
Suburban[¶]	638 (61.9)	573 (79.0)	<0.0001	274 (60.8)	1340 (79.1)	<0.0001
Case detection methods						
Passive case-finding	302 (29.3)	362 (49.9)	<0.0001	286 (63.4)	1046 (61.8)	0.5258
Active case-finding	685 (66.5)	345 (47.6)	<0.0001	151 (33.5)	612 (36.1)	0.2930
Contact investigation	643 (62.4)	122 (16.8)	<0.0001	127 (28.2)	95 (5.6)	<0.0001
Screening high-risk groups	14 (1.4)	205 (28.3)	<0.0001	12 (2.7)	456 (26.9)	<0.0001
Unspecified methods	28 (2.7)	18 (2.5)	0.7609	12 (2.7)	61 (3.6)	0.3268
Unknown	43 (4.2)	18 (2.5)	0.0567	14 (3.1)	35 (2.1)	0.1904
Site of TB						
PTB	342 (33.2)	283 (39.0)	0.0120	255 (56.5)	836 (49.4)	0.0068
EPTB	592 (57.5)	355 (49.0)	0.0004	153 (33.9)	645 (38.1)	0.1032
Mediastinal/hilar lymph node TB	453 (44.0)	190 (26.2)	<0.0001	66 (14.6)	160 (9.5)	0.0014
Other EPTB cases	139 (13.5)	165 (22.8)	<0.0001	87 (19.3)	485 (28.6)	<0.0001
PTB+EPTB	96 (9.3)	87 (12.0)	0.0705	43 (9.5)	212 (12.5)	0.0815
TB status						
New cases	1010 (98.1)	633 (87.3)	<0.0001	426 (94.5)	1429 (84.4)	<0.0001
Relapse cases	2 (0.2)	3 (0.4)	0.3953	8 (1.8)	21 (1.2)	0.3835
Other previously treated cases	1 (0.1)	13 (1.8)	<0.0001	6 (1.3)	36 (2.1)	0.2784
Unknown	17 (1.7)	76 (10.5)	<0.0001	11 (2.4)	207 (12.2)	<0.0001
BCG vaccination						
No	770 (74.8)	158 (21.8)	<0.0001	282 (62.5)	169 (10.0)	<0.0001
Yes	207 (20.1)	373 (51.4)	<0.0001	106 (23.5)	790 (46.7)	<0.0001
Unknown	53 (5.1)	194 (26.8)	<0.0001	63 (14.0)	734 (43.4)	<0.0001
HIV status						
Negative	81 (7.9)	88 (12.1)	0.0028	71 (15.7)	339 (20.0)	0.0399
Positive	1 (0.1)	13 (1.8)	<0.0001	2 (0.4)	28 (1.7)	0.0518
Unknown	948 (92.0)	624 (86.1)	<0.0001	378 (83.8)	1326 (78.3)	0.0103
AFB smear microscopy						
Negative	90 (8.7)	117 (16.1)	<0.0001	79 (17.5)	382 (22.6)	0.0204
Positive	65 (6.3)	88 (12.1)	<0.0001	145 (32.2)	432 (25.5)	0.0048
Unknown/not done	875 (85.0)	520 (71.7)	<0.0001	227 (50.3)	879 (51.9)	0.5490
Mycobacterial culture						
Positive	336 (32.6)	361 (49.8)	<0.0001	314 (69.6)	1302 (76.9)	0.0014
Negative	112 (10.9)	79 (10.9)	0.9880	41 (9.1)	143 (8.4)	0.6642
Unknown/not done	582 (56.5)	285 (39.3)	<0.0001	96 (21.3)	248 (14.6)	0.0006
Drug resistance						
DST done	118 (11.5)	141 (19.4)	<0.0001	144 (31.9)	573 (33.8)	0.4434
Mono/poly H	27 (2.6)	23 (3.2)	0.4944	7 (1.6)	101 (6.0)	0.0001

Continued

TABLE 1 Continued

	Children (0–14 years)			Adolescents (15–19 years)		
	Dutch-born	Foreign-born	p-value	Dutch-born	Foreign-born	p-value
Mono/poly R	0 (0.0)	0 (0.0)	n/a	0 (0.0)	2 (0.1)	1.0000
Mono Z^{+}	6 (0.6)	1 (0.1)	0.2507	4 (0.9)	5 (0.3)	0.0995
MDR	2 (0.2)	8 (1.1)	0.0198	3 (0.7)	24 (1.4)	0.2029
XDR	0 (0.0)	0 (0.0)	n/a	0 (0.0)	1 (0.1)	1.0000

Data are presented as n (%), unless otherwise stated. p-values were calculated using Chi-squared or Fisher's exact tests, where applicable. PTB: pulmonary TB; EPTB: extrapulmonary TB; BCG: Bacille Calmette-Guérin; AFB: acid-fast bacilli; DST: drug susceptibility testing; H: isoniazid; R: rifampicin; Z: pyrazinamide; MDR: multidrug-resistant; XDR: extensively drug-resistant. #: the Hague, Utrecht (city), Amsterdam and Rotterdam; ¶: Groningen, Friesland, Zeeland, Drenthe, Overijssel, Gelderland, Zuid-Holland, Limburg, Utrecht, Noord-Holland, Noord-Brabant, Flevoland or other areas; +: Z and ethambutol resistances were not registered routinely until 2016.

TB notification rates in children declined steadily from 3.8 to 0.7 per 100 000 person-years during 1993–2018 (AAPC −10.9%, 95% CI −12.6–−9.1) (figure 1bi and table 3). Significant decreases were also observed in almost all subgroups of children except for one European-born subgroup (table 3; supplementary figure S3). In adolescents, although the AAPC was not statistically significant, our segmented analysis identified an increasing trend during 1993–2001 and 2012–2018, and a decreasing trend during 2001–2004 (figure 1bii and table 3). Significant average decreases over the whole period were shown in female, Dutch-born, native Dutch, second-generation immigrant, European-born, American-born, Asian-born and urban residing adolescents. In contrast, an increasing trend during 1996–2018 was observed in African-born adolescents (AAPC 18.5%, 95% CI 11.9–25.5). Additionally, our segmented analysis identified recent increasing trends in TB notification rates from 2013–2018 among male adolescents, and from 2012–2018 in both foreign-born and suburban residing adolescents (table 3; supplementary figure S4).

Clinical features

Out of the 3899 study population, 1716 (44.0%) were diagnosed with PTB, 1745 (44.8%) with EPTB and 438 (11.2%) with combined PTB/EPTB. Among 1716 PTB cases, 317 (18.5%) had pulmonary cavitation, and among 2183 patients with EPTB or combined PTB/EPTB, 113 (5.2%) had CNS or miliary TB. Our multivariate analysis revealed that children aged 10–14 years (adjusted (a)OR 20.28, 95% CI 2.71–151.6), adolescents (aOR 23.02, 95% CI 3.15–168.41), symptomatic patients with prolonged patient delay (aOR 2.23, 95% CI 1.35–3.69) and without prolonged patient delay (aOR 1.74, 95% CI 1.07–2.83), those with unknown history of TB contact (aOR 1.95, 95% CI 1.14–3.33) and those with positive mycobacterial cultures (aOR 6.10, 95% CI 2.18–17.08), were associated with increased odds of having cavitary PTB. In contrast, ACF was associated with lower odds of having cavitary PTB (aOR 0.42, 95% CI 0.29–0.60). Furthermore, several groups had increased odds of having CNS or miliary TB, including children aged <2 years (aOR 4.30, 95% CI 1.76–10.54) and aged 2–4 years (aOR 2.88, 95% CI 1.20–6.90), those with culture-confirmed disease (aOR 2.61, 95% CI 1.19–5.70) and those with HIV co-infection (aOR 7.90, 95% CI 2.89–21.62). In contrast, ACF was associated with lower odds of having CNS or miliary TB (aOR 0.12, 95% CI 0.05–0.28) (table 4). In a subgroup analysis of children aged <5 years, those who previously received BCG vaccination had lower odds of having CNS or miliary TB compared to those who were not vaccinated (aOR 0.26, 95% CI 0.07–0.97), adjusted for case-finding methods, history of TB contact and HIV status.

Among 2154 patients with PTB or combined PTB/EPTB, 1392 (64.6%) reported cough. Of these symptomatic patients, 1000 (71.8%) and 1007 (72.3%) had known information on patient and health system delays, respectively. Our multivariate analysis identified that adolescents had a higher odds of prolonged patient delay (aOR 1.81, 95% CI 1.03–3.20) (table 5). Additionally, our subgroup analysis among children showed that unknown history of TB contact was associated with higher odds of prolonged patient delay (aOR 2.17, 95% CI 1.11–4.25), adjusted for year of diagnosis, age, country of birth and area of residence. Several groups including children aged 2–4 years (aOR 2.39, 95% CI 1.07–5.32), females (aOR 1.46, 95% CI 1.07–1.99) and those residing in suburban areas (aOR 1.81, 95% CI 1.25–2.63) had an increased odds of prolonged health system delay. In contrast, patients detected through ACF (aOR 0.51, 95% CI 0.34–0.77) and foreign-born patients with duration of stay <6 months (aOR 0.46, 95% CI 0.26–0.82) were associated with lower odds of prolonged health system delay (table 5).

TABLE 2 Notification rate estimates and notification rate ratios of tuberculosis (TB) among children and adolescents in the Netherlands, 1993–2018

	Overall (1993–2018)				Recent period (2014–2018)	
	Average population	Total number with TB	Notification rate[#] (95% CI)	RR[¶] (95% CI)	Notification rate[#] (95% CI)	RR[¶] (95% CI)
Children						
Total aged 0–14 years	2897182	1755	2.3 (1.8–2.9)	1 (ref)[¶¶]	1.3 (1.0–1.9)	1 (ref)[¶¶]
Age						
<2 years	377873	246	2.4 (1.2–4.6)	1.3 (0.6–2.8)	1.4 (0.6–3.5)	1.5 (0.5–4.3)
2–4 years	576356	387	2.4 (1.4–4.1)	1.3 (0.6–2.6)	1.1 (0.5–2.5)	1.2 (0.4–3.2)
5–9 years	970879	471	1.8 (1.2–2.9)	1 (ref)	1.0 (0.5–1.9)	1 (ref)
10–14 years	972074	651	2.6 (1.7–3.8)	1.4 (0.8–2.6)	1.7 (1.1–2.7)	1.8 (0.8–4.2)
Sex						
Male	1482098	856	2.2 (1.5–3.0)	0.9 (0.6–1.5)	1.2 (0.7–1.9)	0.8 (0.4–1.5)
Female	1415084	899	2.4 (1.7–3.4)	1 (ref)	1.5 (0.9–2.3)	1 (ref)
Origin[+]						
Dutch-born	2812811	852	1.3 (0.9–1.8)	1 (ref)	0.8 (0.5–1.2)	1 (ref)
Foreign born	95083	581	26.3 (17.8–38.9)	20.0 (11.9–33.0)	15.5 (9.3–25.7)	19.1 (9.7–36.4)
Europe[§]	38448	37	2.6 (0.4–18.5)	2.0 (0.1–9.1)	0.0 (0.0–0.0)	n/a[++]
Africa	15412	420	116.8 (73.6–185.4)	88.8 (49.4–153.7)	90.1 (51.2–158.7)	110.9 (53.2–220.3)
America	17565	24	5.7 (0.8–40.4)	4.3 (0.2–19.9)	0.0 (0.0–0.0)	n/a[++]
Asia	22997	99	17.4 (6.5–46.3)	13.2 (4.0–33.0)	7.3 (1.8–29.1)	19.1 (9.7–36.4)
Oceania	660	1	0.0 (0.0–0.0)	n/a[++]	0.0 (0.0–0.0)	n/a[++]
Migration status[+]						
Native Dutch	2247409	228	0.4 (0.2–0.8)	1 (ref)	0.2 (0.1–0.5)	1 (ref)
1st-generation immigrants	95083	581	26.3 (17.8–38.9)	65.7 (31.8–148.8)	15.5 (9.3–25.7)	81.3 (29.5–285.2)
2nd-generation immigrants	565402	601	4.6 (3.1–6.7)	11.5 (5.6–25.9)	2.8 (1.7–4.5)	14.7 (5.4–51.1)
Residence						
Urban[f]	347862	544	5.7 (3.7–8.9)	3.2 (1.8–5.3)	2.1 (1.0–4.2)	1.8 (0.7–3.7)
Suburban[##]	2549313	1211	1.8 (1.3–2.4)	1 (ref)	1.2 (0.8–1.7)	1 (ref)
Adolescents						
Total aged 15–19 years	974620	2144	8.4 (6.8–10.5)	3.6 (2.6–5.0)[¶¶]	6.5 (5.1–8.2)	4.8 (3.2–7.2)[¶¶]
Sex						
Male	498612	1328	10.2 (7.8–13.5)	1.6 (1.0–2.5)	8.2 (6.1–11.1)	1.8 (1.1–3.0)
Female	476008	816	6.5 (4.6–9.3)	1 (ref)	4.6 (3.1–6.9)	1 (ref)
Origin[+]						
Dutch-born	912247	371	1.7 (1.1–2.9)	1 (ref)	1.1 (0.6–2.1)	1 (ref)
Foreign born	67210	1453	93.7 (73.2–120.0)	53.4 (31.7–95.7)	89.4 (68.5–116.8)	78.0 (42.5–157.4)
Europe[§]	22645	75	13.2 (4.3–41.1)	7.6 (1.8–22.7)	4.1 (0.6–29.4)	3.6 (0.2–18.6)
Africa	15163	1122	316.6 (238.6–420.1)	180.5 (104.9–327.8)	447.3 (336.1–595.3)	390.2 (210.3–792.2)
America	13667	41	7.3 (1.0–51.9)	4.2 (0.2–20.4)	0.0 (0.0–0.0)	n/a[++]
Asia	15458	215	58.2 (30.3–111.9)	33.2 (14.0–73.6)	32.8 (13.7–79.0)	28.7 (9.0–78.8)
Oceania	276	0	0.0 (0.0–0.0)	n/a[++]	0.0 (0.0–0.0)	n/a[++]
Migration status[+]						
Native Dutch	760666	123	0.7 (0.3–1.6)	1 (ref)	0.4 (0.1–1.2)	1 (ref)
1st-generation immigrants	67210	1453	93.7 (73.2–120.0)	142.6 (63.4–407.7)	89.4 (68.5–116.8)	231.1 (85.3–948.5)
2nd-generation immigrants	151580	238	6.6 (3.5–12.3)	10.0 (3.6–32.2)	3.8 (1.8–8.0)	9.8 (2.7–45.5)
Residence						
Urban[f]	110038	530	18.2 (11.7–28.2)	2.5 (1.5–4.1)	7.5 (3.9–14.5)	1.2 (0.6–2.3)
Suburban[##]	864577	1614	7.2 (5.6–9.2)	1 (ref)	6.2 (4.8–8.1)	1 (ref)

Data are presented as n, unless otherwise stated. Overall notification rate estimates are presented using data from 1993–2018, unless otherwise stated. RR: rate ratio; n/a: not applicable. [#]: all notification rate estimates are presented per 100 000 person-years; [¶]: notification rate ratios are presented for relative differences between demographic groups. Both notification rates and rate ratios were calculated using Poisson regression models, offset with log population size; [+]: 1996–2018. Population data were derived from the Central Agency for Statistics. Number of TB cases were obtained from the Netherlands Tuberculosis Register; [§]: excluding the Netherlands; [f]: the Hague, Utrecht (city), Amsterdam and Rotterdam; [##]: Groningen, Friesland, Zeeland, Drenthe, Overijssel, Gelderland, Zuid-Holland, Limburg, Utrecht, Noord-Holland, Noord-Brabant, Flevoland or other areas; [¶¶]: adolescents aged 15–19 years were compared to children aged 0–14 years; [++]: mean annual number of TB cases <1; therefore, notification rate ratios were not calculated.

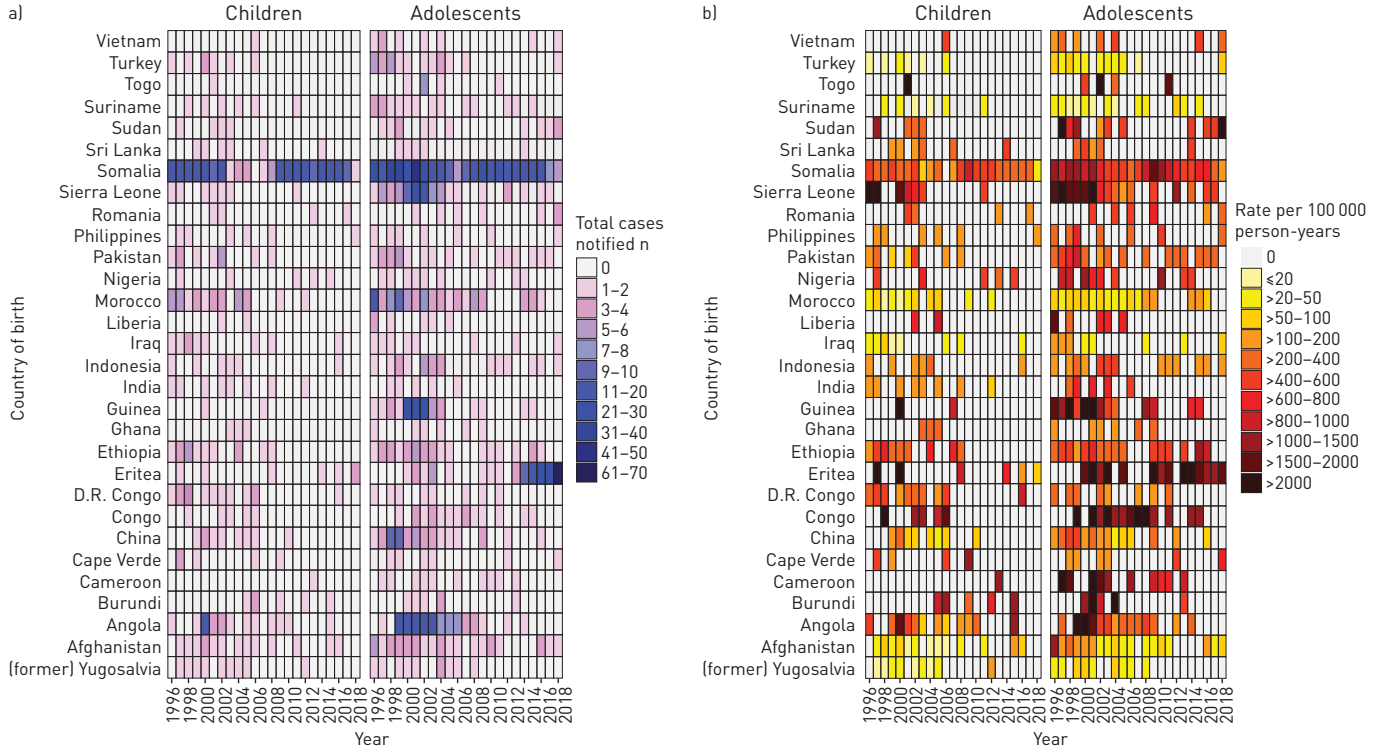

FIGURE 2 Number of annual tuberculosis (TB) cases and notification rate estimates in foreign-born children and adolescents in the Netherlands, stratified by 30 selected countries of birth. a) Number of annual TB cases in foreign-born children and adolescents during 1996–2018; b) TB notification rate estimates per 100 000 person-years in foreign-born children and adolescents during 1996–2018. D.R. Congo: Democratic Republic of Congo.

Bacterial results and drug resistance

Mycobacterial culture results were known in 2688 (68.9%) of 3899 eligible patients, of which 2313 (59.3%) were culture-positive and 375 (9.6%) were culture-negative. Mycobacterial culture was more likely to be positive in adolescents (aOR 1.93, 95% CI 1.25–2.98), among foreign-born (aOR 1.40, 95% CI 1.05–1.88), those reporting cough (aOR 1.79, 95% CI 1.29–2.45), those detected through PCF (aOR 4.86, 95% CI 3.54–6.66), those with PTB (aOR 8.42, 95% CI 5.90–12.02) and with combined PTB/EPTB (aOR 4.13, 95% CI 2.65–6.43) (supplementary table S2). DST results were available in 976 (42.2%) of 2313 patients with culture-confirmed TB. Of these, isoniazid- and rifampicin-resistant, MDR and extensively drug-resistant isolates were observed in 158 (16.2%), two (0.2%), 37 (3.8%) and one (0.1%), respectively. Additionally, 1337 (57.8%) of 2313 culture-confirmed TB cases had missing information on DST results; of these, 1321 (98.8%) were notified before 2005 (supplementary figure S5). Detection of MDR-TB was more likely to be higher in patients detected through ACF (aOR 2.26, 95% CI 1.11–4.61) and in re-treated TB cases (aOR 8.54, 95% CI 2.55–28.55) (supplementary table S3).

Discussion

The overall TB notification rate among children in our study was relatively low, and is comparable to those reported in other low TB incidence countries such as the UK, Australia, Canada and the USA, with overall rates ranging from 1.0 to 4.3 per 100 000 person-years [20–24]. Almost all subgroups of children in our study had declining trends in TB notification during the study period. Although a declining trend was also shown in foreign-born children, disproportionately higher rates compared to Dutch-born children were observed in this population, particularly those from Africa. Previous reports from the UK and Denmark support that childhood TB burden among the African immigrant population is higher compared to other immigrant groups [22, 25]. In adolescents, the annual number of foreign-born TB cases has consistently exceeded Dutch-born patients since 1993; this mirrors the trends in the adult population with TB [26]. Although Dutch-born adolescents had declining trends of TB notification, an increasing trend was observed in the foreign-born group, especially those from Africa. This might be explained by the increased number of (unaccompanied) minor asylum seekers coming to the Netherlands in recent years.

Our study showed a high number of TB cases notified among Somali-born children and adolescents over the whole period, with an additional high TB caseload among Eritrean-born adolescents in recent years.

TABLE 3 Trends in tuberculosis (TB) notification rates in children and adolescents in the Netherlands, 1993–2018

	Trend 1		Trend 2		Trend 3		Trend 4		Trend 5		AAPC, 1993–2018 (95% CI)[#]
	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC	
Children											
Total aged 0–14 years	1993–2007	−14.9[++]	2007–2018	−5.4							−10.9% (−12.6–−9.1)[++]
Age											
<2 years	1993–2014	−13.8[++]	2014–2018	27.0							−8.3% (−13.7–−2.5)[++]
2–4 years	1993–1999	−3.4	1999–2018	−13.8[++]							−11.4% (−15.6–−7.0)[++]
5–9 years	1993–2000	−17.6[++]	2000–2018	−7.3[++]							−10.5 (−13.1–−7.9)[++]
10–14 years	1993–2000	−5.4	2000–2005	−33.2[++]	2005–2018	−1.3					−9.8% (−12.9–−6.5)[++]
Sex											
Male	1993–1999	−2.0	1999–2005	−23.1[++]	2005–2018	−4.7					−8.8% (−11.2–−6.2)[++]
Female	1993–2007	−16.6[++]	2007–2018	−4.1							−11.3% (−13.8–−8.8)[++]
Origin[¶]											
Dutch-born	1996–2018	−6.3[++]									−6.3% (−8.0–−4.5)[++]
Native Dutch	1996–2000	−14.4[++]	2000–2018	−1.8[++]							−4.4% (−5.6–−3.3)[++]
2[nd]-generation immigrants	1996–2010	−6.9[++]	2010–2018	−12.9							−22.1% (−28.8–−14.8)[++]
Foreign-born[+]	1996–1999	15.7	1999–2006	−34.5[++]	2006–2011	51.1	2011–2018	−25.2[++]			−11.5% (−16.6–−6.1)[++]
Europe[+,§]	1996–2000	25.6[++]	2000–2005	−17.0[++]	2005–2018	−0.8					0.4 (−1.8–2.7)
Africa[+]	1996–2000	84.2	2000–2006	−78.6[++]	2006–2011	1938.4[++]	2011–2018	−84.0[++]			−30.6% (−46.8–−9.6)[++]
America[+]	1996–2018	−2.9[++]									−2.9% (−6.4–−0.8)[++]
Asia[+]	1996–2010	−19.2[++]	2010–2018	−2.9							−13.6% (−19.3–−7.6)[++]
Residence											
Urban[##]	1993–1999	64.2	1999–2005	−67.6[++]	2005–2018	−22.9					−24.9% (−34.6–−13.8)[++]
Suburban[¶¶]	1993–2006	−12.4[++]	2006–2018	−2.4							−7.7% (−9.0–−6.4)[++]
Adolescents											
Total aged 15–19 years	1993–2001	104.7[++]	2001–2004	−95.3[++]	2004–2012	−24.2	2012–2018	130.3[++]			−5.8% (−15.6–5.1)
Sex											
Male	1993–2001	229.1[++]	2001–2004	−99.2[++]	2004–2013	−36.0	2013–2018	499.7[++]			4.8% (−11.7–24.5)
Female	1993–2001	24.2	2001–2006	−79.0[++]	2006–2018	14.2					−14.2% (−20.4–−7.4)[++]
Origin[¶]											
Dutch-born	1996–1997	−67.3	1997–2006	4.0	2006–2008	−45.9	2008–2018	2.7			−11.9% (−16.6–−7.0)[++]
Native Dutch	1996–1998	−54.7	1998–2011	−7.1[++]	2011–2018	10.7					−8.7% (−11.9–−5.3)[++]
2nd generation immigrants	1996–2006	−11.4	2006–2008	−81.3	2008–2018	−18.5					−26.0% (−38.6–−11.0)[++]
Foreign born[+]	1996–2001	436.1[++]	2001–2005	−96.5[++]	2005–2009	139.7	2009–2012	−50.7	2012–2018	246.3[++]	7.1% (−9.1–26.1)
Europe[+,§]	1996–2005	−3.4	2005–2009	−46.9	2009–2018	6.4					−8.4% (−15.6–−0.6)[++]
Africa[f]	1996–2001	111.2[++]	2001–2004	−70.8[++]	2004–2009	69.5[++]	2009–2012	−32.2	2012–2018	79.3[++]	18.5% (11.9–25.5)[++]
America[+]	1996–1997	−83.9	1997–2018	−3.2							−12.9% (−19.5–−5.7)[++]
Asia[+]	1996–2006	−79.5[++]	2006–2018	19.0							−47.6% (−57.0–−36.1)[++]
Residence											
Urban[##]	1993–1999	663.8[++]	1999–2008	−93.7[++]	2008–2018	−28.9					−47.9% (−61.5–−29.5)[++]
Suburban[¶¶]	1993–2001	93.7[++]	2001–2004	−97.5[++]	2004–2012	−17.5	2012–2018	157.7[++]			1.5% (−10.3–14.9)

APC: annual percentage changes from the segmented linear regression analysis; AAPC: average annual percentage changes. Population estimates were derived from the Central Agency for Statistics, and number of TB cases were obtained from the Netherlands Tuberculosis Register. [#]: AAPCs were based on the summary estimates of segmented linear regression analysis over the entire data series from 1993–2018, unless otherwise stated; [¶]: 1996–2018; [+]: per 10 000 person-years; [§]: excluding the Netherlands; [f]: per 1000 person-years; [##]: the Hague, Utrecht (city), Amsterdam and Rotterdam; [¶¶]: Groningen, Friesland, Zeeland, Drenthe, Overijssel, Gelderland, Zuid-Holland, Limburg, Utrecht, Noord-Holland, Noord-Brabant, Flevoland or other areas; [++]: APC or AAPC is significantly different from zero (two-sided p<0.05). Based on the best-improved confidence intervals for AAPC, we used TB notification rate estimates per 100 000 person-years, unless otherwise stated.

TABLE 4 Final model for factors associated with severe forms of tuberculosis (TB) in children and adolescents in the Netherlands, 1993–2018

	Model-1 (PTB only)[#]						Model-2 (EPTB or combined PTB/EPTB)[¶]					
	Severe[+]	Less-severe[§]	cOR (95% CI)	p-value	aOR (95% CI)	p-value	Severe[f]	Less-severe[##]	cOR (95% CI)	p-value	aOR (95% CI)	p-value
Cases	317	1212					113	1974				
Age												
<2 years	1 (0.3)	84 (6.9)	1.25 (0.08–20.28)	0.8753	1.03 (0.06–17.11)	0.9807	15 (13.3)	123 (6.2)	3.82 (1.67–8.73)	0.0015	4.30 (1.76–10.54)	0.0014
2–4 years	1 (0.3)	103 (8.5)	1.02 (0.06–16.52)	0.9892	1.00 (0.06–16.50)	0.9994	15 (13.3)	240 (12.2)	1.96 (0.86–4.43)	0.1077	2.88 (1.20–6.90)	0.0179
5–9 years	1 (0.3)	105 (8.7)	1.00		1.00		10 (8.8)	313 (15.9)	1.00		1.00	
10–14 years	50 (15.8)	179 (14.8)	29.33 (3.99–215.44)	0.0009	20.28 (2.71–151.61)	0.0034	22 (19.5)	354 (17.9)	1.94 (0.91–4.17)	0.0873	1.07 (0.48–2.38)	0.8595
15–19 years	264 (83.3)	741 (61.1)	37.41 (5.19–269.40)	0.0003	23.02 (3.15–168.41)	0.0020	51 (45.1)	944 (47.8)	1.69 (0.85–3.37)	0.1355	0.55 (0.26–1.13)	0.1044
Types of case-finding												
Active	73 (23.0)	727 (60.0)	0.19 (0.14–0.26)	<0.0001	0.42 (0.29–0.60)	<0.0001	8 (7.1)	834 (42.2)	0.10 (0.05–0.22)	<0.0001	0.12 (0.05–0.28)	<0.0001
Passive	236 (74.4)	455 (37.5)	1.00		1.00		100 (88.5)	1088 (55.1)	1.00		1.00	
Unknown	8 (2.5)	30 (2.5)	0.51 (0.23–1.14)	0.1012	1.27 (0.50–3.20)	0.6167	5 (4.4)	52 (2.6)	1.04 (0.41–2.68)	0.9251	0.93 (0.32–2.70)	0.8879
Mycobacterial culture												
Positive	303 (95.6)	878 (72.4)	9.40 (3.44–25.72)	<0.0001	6.10 (2.18–17.08)	0.0006	90 (79.6)	911 (46.1)	3.09 (1.48–6.45)	0.0027	2.61 (1.19–5.70)	0.0165
Negative	4 (1.3)	109 (9.0)	1.00		1.00		8 (7.1)	250 (12.7)	1.00		1.00	
Unknown/not done	10 (3.2)	225 (18.6)	1.21 (0.37–3.95)	0.7508	1.79 (0.53–6.01)	0.3449	15 (13.3)	813 (41.2)	0.58 (0.24–1.38)	0.2146	0.69 (0.27–1.72)	0.4263
Presence of TB symptoms												
No	40 (12.6)	478 (39.4)	1.00		1.00							
Yes, patient delay ⩽4 weeks	115 (36.3)	326 (26.9)	4.21 (2.86–6.20)	<0.0001	1.74 (1.07–2.83)	0.0262						
Yes, patient delay >4 weeks	88 (27.8)	180 (14.9)	5.84 (3.87–8.81)	<0.0001	2.23 (1.35–3.69)	0.0017						
Yes, unknown delay	69 (21.8)	209 (17.2)	3.94 (2.56–6.02)	<0.0001	1.95 (1.18–3.22)	0.0092						
Unknown	5 (1.6)	19 (1.6)	3.14 (1.11–8.87)	0.0303	1.86 (0.59–5.89)	0.2909						
Known history of TB contact												
No	298 (94.0)	846 (69.8)	6.78 (4.20–10.96)	<0.0001	1.95 (1.14–3.33)	0.0141						
Yes	19 (6.0)	366 (30.2)	1.00		1.00							
HIV status												
Negative							24 (21.2)	304 (15.4)	1.00		1.00	
Positive							9 (8.0)	18 (0.9)	6.33 (2.57–15.60)	<0.0001	7.90 (2.89–21.62)	<0.0001
Unknown							80 (70.8)	1652 (83.7)	0.61 (0.38–0.98)	0.0425	0.59 (0.36–0.98)	0.0419

Data are presented as n or n (%), unless otherwise stated. PTB: pulmonary TB; EPTB: extrapulmonary TB; cOR crude odds ratio; aOR adjusted odds ratio. [#]: included patients with PTB only; [¶]: included patients with EPTB or combined PTB/EPTB; [+]: included cavitary PTB cases; [§]: included PTB cases without the presence of pulmonary cavitation; [f]: included patients with central nervous system (CNS) TB or miliary TB; [##]: included patients with EPTB or combined PTB/EPTB other than CNS TB and miliary TB. Hosmer–Lemeshow test: model 1 p=0.955, model 2 p=0.665. Area under the receiver operating characteristic curves (95% CI): model 1 0.79 (0.76–0.81), model 2 0.79 (0.75–0.83). Patients born outside the Netherlands, who previously received bacille Calmette–Guérin vaccination, and those who were smear-positive for sputum or bronchoalveolar lavage (BAL) were significantly associated with increased odds of having cavitary PTB in univariate analysis, but did not remain significant in multivariate analysis. Furthermore, patients who experienced TB symptoms (persistent cough), with unknown history of TB contact and with smear-positive for sputum/BAL had a significantly increased odds of having CNS or miliary TB in univariate analysis, but did not retain significant in multivariate analysis.

TABLE 5 Final model for factors associated with prolonged patient delay and health system delay in children and adolescents with tuberculosis (TB) in the Netherlands, 1993–2018

	Model 1 (patient delay)[#]						Model 2 (health system delay)[¶]					
	>4 weeks	⩽4 weeks	cOR (95% CI)	p-value	aOR (95% CI)	p-value	>4 weeks	⩽4 weeks	cOR (95% CI)	p-value	aOR (95% CI)	p-value
Cases	372	628					237	770				
Year of diagnosis												
1993–1998	131 (35.2)	228 (36.3)	1.74 (1.12–2.70)	0.0133	1.87 (1.18–2.95)	0.0072	110 (46.4)	293 (38.1)	2.38 (1.43–3.96)	0.0009	2.49 (1.47–4.23)	0.0007
1999–2003	131 (35.2)	142 (22.6)	2.79 (1.78–4.38)	<0.0001	2.87 (1.80–4.57)	<0.0001	57 (24.1)	175 (22.7)	2.06 (1.19–3.57)	0.0097	2.03 (1.15–3.58)	0.0144
2004–2008	55 (14.8)	92 (14.6)	1.81 (1.09–3.01)	0.0219	1.95 (1.15–3.31)	0.0135	31 (13.1)	107 (13.9)	1.83 (1.00–3.38)	0.0510	1.65 (0.87–3.12)	0.1215
2009–2013	20 (5.4)	60 (9.6)	1.01 (0.53–1.90)	0.9766	1.05 (0.55–2.00)	0.8878	18 (7.6)	62 (8.1)	1.84 (0.91–3.69)	0.0872	1.79 (0.87–3.67)	0.1106
2014–2018	35 (9.4)	106 (16.9)	1.00		1.00		21 (8.9)	133 (17.3)	1.00		1.00	
Age												
<2 years	7 (1.9)	40 (6.4)	0.52 (0.20–1.34)	0.1751	0.45 (0.17–1.22)	0.1177	11 (4.6)	35 (4.5)	1.39 (0.57–3.39)	0.4674	1.44 (0.57–3.65)	0.4392
2–4 years	18 (4.8)	37 (5.9)	1.43 (0.67–3.09)	0.3570	1.56 (0.71–3.42)	0.2644	22 (9.3)	45 (5.8)	2.16 (1.00–4.69)	0.0499	2.39 (1.07–5.32)	0.0332
5–9 years	19 (5.1)	56 (8.9)	1.00		1.00		14 (5.9)	62 (8.1)	1.00		1.00	
10–14 years	62 (16.7)	105 (16.7)	1.74 (0.95–3.20)	0.0739	1.65 (0.88–3.09)	0.1188	43 (18.1)	130 (16.9)	1.46 (0.75–2.88)	0.2675	1.31 (0.65–2.66)	0.4525
15–19 years	266 (71.5)	390 (62.1)	2.01 (1.17–3.46)	0.0117	1.81 (1.03–3.20)	0.0403	147 (62.0)	498 (64.7)	1.31 (0.71–2.40)	0.3881	1.28 (0.67–2.43)	0.4531
Immigrants or asylum seekers												
No	109 (29.3)	232 (36.9)	1.00		1.00		82 (34.6)	253 (32.9)	1.00		1.00	
Yes, duration <6 months	74 (19.9)	92 (14.6)	1.71 (1.17–2.51)	0.0057	1.41 (0.94–2.14)	0.0991	19 (8.0)	153 (19.9)	0.38 (0.22–0.66)	0.0005	0.46 (0.26–0.82)	0.0082
Yes, duration 6–29 months	69 (18.5)	138 (22.0)	1.06 (0.74–1.54)	0.7402	0.82 (0.55–1.23)	0.3424	57 (24.1)	159 (20.6)	1.11 (0.75–1.64)	0.6141	1.13 (0.74–1.74)	0.5648
Yes, duration 2.5–5 years	64 (17.2)	75 (11.9)	1.82 (1.21–2.72)	0.0038	1.33 (0.87–2.04)	0.1930	35 (14.8)	103 (13.4)	1.05 (0.66–1.66)	0.8394	0.97 (0.59–1.58)	0.8921
Yes, duration ⩾5 years	39 (10.5)	65 (10.4)	1.28 (0.81–2.02)	0.2949	0.90 (0.55–1.45)	0.6608	27 (11.4)	68 (8.8)	1.22 (0.73–2.04)	0.4359	1.12 (0.65–1.92)	0.6909
Yes, duration unknown	17 (4.6)	26 (4.1)	1.39 (0.72–2.67)	0.3207	0.98 (0.50–1.93)	0.9584	17 (7.2)	34 (4.4)	1.54 (0.82–2.91)	0.1796	1.33 (0.68–2.60)	0.4074
Known history of TB contact												
No	335 (90.1)	513 (81.7)	2.03 (1.37–3.01)	0.0004	1.51 (0.98–2.33)	0.0608						
Yes	37 (9.9)	115 (18.3)	1.00		1.00							
Sex												
Male							118 (49.8)	468 (60.8)	1.00		1.00	
Female							119 (50.2)	302 (39.2)	1.56 (1.17–2.09)	0.0028	1.46 (1.07–1.99)	0.0157
Residential area												
Urban[+]							49 (20.7)	207 (26.9)	1.00		1.00	
Suburban[§]							188 (79.3)	563 (73.1)	1.41 (0.99–2.01)	0.0556	1.81 (1.25–2.63)	0.0017
Type of case-finding												
Active							43 (18.1)	245 (31.8)	0.47 (0.33–0.68)	<0.0001	0.51 (0.34–0.77)	0.0013
Passive							192 (81.0)	517 (67.1)	1.00		1.00	
Unknown							2 (0.8)	8 (1.0)	0.67 (0.14–3.20)	0.6187	0.60 (0.12–2.97)	0.5337

Data are presented as n or n (%), unless otherwise stated. cOR crude odds ratio; aOR adjusted odds ratio; PTB: pulmonary TB; EPTB: extrapulmonary TB. [#]: the time interval from the onset of TB symptoms to the patient's first consultation with healthcare provider related to this TB episode (applicable for symptomatic patients with PTB or combined PTB/EPTB); [¶]: the time interval from the patient's first consultation with healthcare provider to the initiation of TB treatment (applicable for symptomatic patients with PTB or combined PTB/EPTB). A cut-off of >4 weeks was used to define either prolonged patient delay or health system delay; [+]: the Hague, Utrecht (city), Amsterdam and Rotterdam; [§]: Groningen, Friesland, Zeeland, Drenthe, Overijssel, Gelderland, Zuid-Holland, Limburg, Utrecht, Noord-Holland, Noord-Brabant, Flevoland or other areas. Hosmer–Lemeshow test: model 1 p=0.884, model 2 p=0.250. Area under the receiver operating characteristic curves (95% CI): model 1 0.64 (0.61–0.68), model 2 0.67 (0.63–0.71). Foreign-born patients had a significantly increased odds of prolonged patient delay in univariate analysis, but did not remain significant in multivariate analysis. Furthermore, patients with unknown history of TB contact had a significantly increased odds of prolonged health system delay in univariate analysis, but did not retain significance in multivariate analysis.

TB incidence among Eritrean and Somalian asylum seekers is high, not only at entry screening, but also within the first 5 years after arrival in the Netherlands [27]. Irrespective of the year of diagnosis, our study showed that approximately one-third of the foreign-born patients were detected within 6 months after arrival, while approximately two-thirds of the foreign-born patients were detected after 6 months of arrival. The latter is probably attributable to reactivation of TB infection in their country of origin [28], or exposure to TB during travel to the Netherlands [29]. This may also be explained by recent transmission within specific communities [28, 30], such as clustered patients coming from sub-Saharan Africa or living in an urban area [30].

In the Netherlands, entry screening for TB by chest radiography is currently mandatory for new immigrants from countries with TB incidence >100 per 100 000 population and for asylum seekers from countries with TB incidence >50 per 100 000 population. Additionally, immigrants and asylum seekers from countries with TB incidence ⩾200 per 100 000 population are offered voluntary biannual follow-up screening for a 2-year period [31]. Evidently, the current screening approach is not sufficient to reduce TB incidence in these migrant populations. Introducing universal screening for latent TB infection (LTBI) and preventive treatment for immigrants and asylum seekers from high TB incidence countries might prevent TB disease [32, 33]. This practice has been implemented in the Netherlands since 2016 as entry screening for immigrants aged <18 years, but not yet for all asylum seekers, due to operational challenges [31, 34]. Implementation of LTBI screening and treatment in both immigrants and asylum seekers on arrival in the Netherlands is feasible and effective [35, 36]. Adequate resources as well as community engagement involving well-connected and trusted community members as facilitators are needed to reach and motivate this population for LTBI screening and treatment programmes [37]. Radiographic screening for asylum seekers aged <12 years is not effective [38]; therefore, LTBI screening and treatment would be a preferable intervention in this group.

Children with TB infection not receiving preventive therapy have an increased risk of developing TB disease within 2 years after exposure, and the risk is highest among children aged <5 years [39]. This reinforces the need for immediate contact investigations. In our study, most of the TB cases in children aged <10 years and in Dutch-born children were detected through ACF using contact investigations. However, many of the TB cases among Dutch- and foreign-born adolescents were detected through PCF. In a study among children from 2005–2012, foreign-born children who had lived in the Netherlands for >6 months were significantly more often detected through PCF than by ACF [14]. This association is no longer significant in our subgroup analysis using recent data from 2012–2018 (results not shown). The improvement of eligibility for LTBI screening among child and adolescent TB contacts since 2012, may have resulted in more foreign-born TB contacts being screened and treated for LTBI [40]. It can be assumed that there has been less transmission within these population groups in recent years, and more TB disease being prevented through LTBI treatment of TB contacts.

Beyond benefits of ACF to enhance TB case detection and reduce transmission, our results provide evidence for additional advantages of ACF to reduce severe forms of TB and decrease health system delay. In low- and middle-income countries, ACF among household contacts of patients with TB is effective in enhancing TB case detection [41, 42], and reducing all-cause mortality [41]. In the Netherlands, ACF interventions also benefit children and adolescents in improving TB treatment outcomes, particularly in reducing all-cause mortality [4]. However, it should be acknowledged that even in a setting where ACF is well implemented like the Netherlands, missed opportunities for prevention persist. Erkens *et al.* [14] reported that among 37% childhood TB cases, there was at least one missed opportunity for prevention, and of children eligible for BCG vaccination, 39% were not vaccinated.

The strength of this study is the inclusion of a relatively long duration of data series, making it possible to perform a robust time-series analysis and provide a complete picture of TB epidemiology in different demographic groups. Our study has some limitations. All patients are assumed to have been notified to the NTR, but the possibility of undernotification cannot be ruled out, particularly during the earlier period of registration. In 1998, the adjusted undernotification of TB was 7.3%, and those with non-culture-confirmed TB were less likely to be notified [43]. In 2005, a central web-based registration system was introduced and laboratory results were matched with the NTR in real time. After these improvements, we expect that the completeness of TB notification has increased over time. Although some EPTB cases such as abdominal TB, osteoarticular TB and urogenital TB could be life-threatening, these forms of EPTB were assumed to be less severe than CNS and miliary TB in our study because EPTB cases other than CNS and miliary TB were not associated with higher risk of mortality in our previous analysis [4]. In addition, this study is limited by its retrospective nature with partly incomplete records for some of the variables. As an example, DST results were not systematically registered until 2005, causing >98% of the culture-confirmed TB cases before 2005 to have missing information on drug-susceptibility status.

Therefore, to minimise selection bias in analysing factors associated with MDR-TB, year of diagnosis was included as one of the explanatory variables in the multivariate model.

In conclusion, TB notification rates in children were relatively low across different demographic groups and have decreased to pre-elimination level among native Dutch children. However, substantially higher rates were found among foreign-born adolescents, particularly those from Africa. Optimising current TB control programmes by enhancing ACF, including contact investigations and screening for TB and LTBI in foreign-born children and adolescents, may be the best way forward to reduce the TB burden in these high-risk groups.

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References

1 World Health Organization (WHO). Global Tuberculosis Report 2019. Geneva, WHO, 2019. Available from: www.who.int/tb/publications/global_report/en/ Date last accessed: April 6, 2020.
2 Dodd PJ, Yuen CM, Sismanidis C, *et al.* The global burden of tuberculosis mortality in children: a mathematical modelling study. *Lancet Glob Heal* 2017; 5: e898–e906.
3 Jenkins HE, Yuen CM, Rodriguez CA, *et al.* Mortality in children diagnosed with tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2017; 17: 285–295.
4 Gafar F, Van't Boveneind-Vrubleuskaya N, Akkerman OW, *et al.* Nationwide analysis of treatment outcomes in children and adolescents routinely treated for tuberculosis in The Netherlands. *Eur Respir J* 2019; 54: 1901402.
5 Osman M, Lee K, Du Preez K, *et al.* Excellent treatment outcomes in children treated for tuberculosis under routine operational conditions in Cape Town, South Africa. *Clin Infect Dis* 2017; 65: 1444–1452.
6 Reuter A, Hughes J, Furin J. Challenges and controversies in childhood tuberculosis. *Lancet* 2019; 394: 967–978.
7 Gröschel MI, van den Boom M, Migliori GB, *et al.* Prioritising children and adolescents in the tuberculosis response of the WHO European Region. *Eur Respir Rev* 2019; 28: 180106.
8 Marais BJ, Schaaf HS, Graham SM. Child health and tuberculosis. *Lancet Respir Med* 2014; 2: 254–256.
9 Snow KJ, Sismanidis C, Denholm J, *et al.* The incidence of tuberculosis among adolescents and young adults: a global estimate. *Eur Respir J* 2018; 51: 1702352.
10 Snow KJ, Cruz AT, Seddon JA, *et al.* Adolescent tuberculosis. *Lancet Child Adolesc Heal* 2020; 4: 68–79.
11 García-Basteiro AL, Schaaf HS, Diel R, *et al.* Adolescents and young adults: a neglected population group for tuberculosis surveillance. *Eur Respir J* 2018; 51: 1800176.
12 Marais BJ, Amanullah F, Gupta A, *et al.* Tuberculosis in children, adolescents, and women. *Lancet Respir Med* 2020; 8: 335–337.
13 Pareek M, Greenaway C, Noori T, *et al.* The impact of migration on tuberculosis epidemiology and control in high-income countries: a review. *BMC Med* 2016; 14: 48.
14 Erkens CG, de Vries G, Keizer ST, *et al.* The epidemiology of childhood tuberculosis in the Netherlands: still room for prevention. *BMC Infect Dis* 2014; 14: 295.
15 European Centre for Disease Prevention and Control/World Health Organizationn Regional Office for Europe. Tuberculosis Surveillance and Monitoring in Europe 2020–2018 data. Copenhagen, Denmark; 2019. www.ecdc.europa.eu/en/publications-data/tuberculosis-surveillance-and-monitoring-europe-2020-2018-data Date last accessed: May 22, 2020.
16 World Health Organization (WHO). Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children. 2nd Edn. WHO, 2014. www.who.int/tb/publications/childtb_guidelines/en/ Date last accessed: May 22, 2020.
17 Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC Public Health* 2008; 8: 15.
18 Clegg LX, Hankey BF, Tiwari R, *et al.* Estimating average annual per cent change in trend analysis. *Stat Med* 2009; 28: 3670–3682.

19 De Vries G, Riesmeijer R. National Tuberculosis Control Plan 2016–2020: Towards Elimination. Bilthoven: National Institute for Public Health and the Environment, 2016. www.rivm.nl/bibliotheek/rapporten/2016-0012.pdf Date last accessed: May 11, 2020.
20 Teo SS, Tay EL, Douglas P, *et al.* The epidemiology of tuberculosis in children in Australia, 2003–2012. *Med J Aust* 2015; 203: 440.
21 Cowger TL, Wortham JM, Burton DC. Epidemiology of tuberculosis among children and adolescents in the USA, 2007–17: an analysis of national surveillance data. *Lancet Public Health* 2019; 4: e506–e516.
22 Abubakar I, Laundy MT, French CE, *et al.* Epidemiology and treatment outcome of childhood tuberculosis in England and Wales: 1999–2006. *Arch Dis Child* 2008; 93: 1017–1021.
23 Dhawan V, Bown J, Lau A, *et al.* Towards the elimination of paediatric tuberculosis in high-income, immigrant-receiving countries: a 25-year conventional and molecular epidemiological case study. *ERJ Open Res* 2018; 4: 00131-2017.
24 Menzies HJ, Winston CA, Holtz TH, *et al.* Epidemiology of tuberculosis among US- and foreign-born children and adolescents in the United States, 1994–2007. *Am J Public Health* 2010; 100: 1724–1729.
25 Hatleberg CI, Prahl JB, Rasmussen JN, *et al.* A review of paediatric tuberculosis in Denmark: 10-year trend, 2000–2009. *Eur Respir J* 2014; 43: 863–871.
26 Slump E, Erkens C, Van Hunen R, *et al.* Tuberculose in Nederland 2018 – Surveillancerapport [Tuberculosis in the Netherlands 2018 – Surveillance Report]. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu, 2019. www.rivm.nl/bibliotheek/rapporten/2019-0188.pdf Date last accessed: April 6, 2020.
27 van den Boogaard J, Slump E, Schimmel HJ, *et al.* High incidence of active tuberculosis in asylum seekers from Eritrea and Somalia in the first 5 years after arrival in the Netherlands. *Emerging Infect Dis* 2020; 26: 675–681.
28 De Vries G, Baars HWM, Šebek MMGG, *et al.* Transmission classification model to determine place and time of infection of tuberculosis cases in an urban area. *J Clin Microbiol* 2008; 46: 3924–3930.
29 Jajou R, De Neeling A, Rasmussen EM, *et al.* A predominant variable-number tandem-repeat cluster of *Mycobacterium tuberculosis* isolates among asylum seekers in the Netherlands and Denmark, deciphered by whole-genome sequencing. *J Clin Microbiol* 2018; 56: e01100-17.
30 Kik SV, Verver S, van Soolingen D, *et al.* Tuberculosis outbreaks predicted by characteristics of first patients in a DNA fingerprint cluster. *Am J Respir Crit Care Med* 2008; 178: 96–104.
31 Commissie voor Praktische Tuberculosebestrijding. Beleid Screening Asielzoekers en Immigranten [Policy for Screening Asylum Seekers and Immigrants]. The Hague, KNCV Tuberculosis Foundation, 2019. www.kncvtbc.org/uploaded/2019/05/6.13_risicogroepenbeleid.pdf Date last accessed: April 6, 2020.
32 Mueller-Hermelink M, Kobbe R, Methling B, *et al.* Universal screening for latent and active tuberculosis (TB) in asylum seeking children, Bochum and Hamburg, Germany, September 2015 to November 2016. *Euro Surveill* 2018; 23: 17-00536.
33 Colgan K, Anderson J, Maycock A, *et al.* Latent tuberculosis may be missed by current screening practices: analysis of interferon-gamma release assay results from a paediatric refugee clinic. *J Paediatr Child Health* 2019; 55: 826–832.
34 Erkens CGM, Slump E, Verhagen M, *et al.* Monitoring latent tuberculosis infection diagnosis and management in the Netherlands. *Eur Respir J* 2016; 47: 1492–1501.
35 Spruijt I, Erkens C, Suurmond J, *et al.* Implementation of latent tuberculosis infection screening and treatment among newly arriving immigrants in the Netherlands: a mixed methods pilot evaluation. *PLoS One* 2019; 14: e0219252.
36 Spruijt I, Tesfay Haile D, Suurmond J, *et al.* Latent tuberculosis screening and treatment among asylum seekers: a mixed methods study. *Eur Respir J* 2019; 54: 1900861.
37 Spruijt I, Haile DT, Erkens C, *et al.* Strategies to reach and motivate migrant communities at high risk for TB to participate in a latent tuberculosis infection screening program: a community-engaged mixed methods study among Eritreans. *BMC Public Health* 2020; 20: 315.
38 Wolters BA, Akkerman OW, Aartsma Y, *et al.* Impact of radiographic screening of >34 000 asylum seeker children. *Eur Respir J* 2019; 54: 1900579.
39 Martinez L, Cords O, Horsburgh CR, *et al.* The risk of tuberculosis in children after close exposure: a systematic review and individual-participant meta-analysis. *Lancet* 2020; 395: 973–984.
40 van Rest J, Erkens C, de Vries G. Evaluatie bron- en contactonderzoek bij tuberculosepatiënten in Nederland. [Evaluation of source and contact investigation in tuberculosis patients in the Netherlands]. *Tegen Tuberc* 2014; 110: 3–6.
41 Fox GJ, Nhung NV, Sy DN, *et al.* Household-contact investigation for detection of tuberculosis in Vietnam. *N Engl J Med* 2018; 378: 221–229.
42 Saunders MJ, Tovar MA, Collier D, *et al.* Active and passive case-finding in tuberculosis-affected households in Peru: a 10-year prospective cohort study. *Lancet Infect Dis* 2019; 19: 519–528.
43 van Hest NAH, Smit F, Baars HM, *et al.* Completeness of notification of tuberculosis in The Netherlands: how reliable is record-linkage and capture–recapture analysis? *Epidemiol Infect* 2007; 135: 1021–1029.