Monitoring latent tuberculosis infection diagnosis and management in the Netherlands

Connie G.M. Erkens[1], Erika Slump[2], Maurits Verhagen[3], Henrieke Schimmel[2], Gerard de Vries[1,2], Frank Cobelens[1,4] and Susan van den Hof[1,4]

Affiliations:
[1]KNCV Tuberculosis Foundation, The Hague, The Netherlands.
[2]Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, The Netherlands.
[3]Municipal Public Health Service (GGD) Limburg-Noord, Roermond, The Netherlands.
[4]Dept of Global Health, Academic Medical Center, Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands.

Correspondence:
Connie G.M. Erkens, KNCV Tuberculosis Foundation, PB 146, 2501 CC The Hague, The Netherlands.
E-mail: Connie.erkens@kncvtbc.org

ABSTRACT Targeted diagnosis and treatment of latent tuberculosis (TB) infection (LTBI) among persons with a high risk of exposure to TB or of developing TB when infected has been performed and monitored routinely in the Netherlands since 1993. We describe trends in target groups, diagnostic methods and treatment regimens, and explore determinants for treatment initiation, treatment completion and adverse events.

In total, 37 729 persons were registered with LTBI from 1993 to 2013, of whom 28 931 (77%) started preventive treatment; 82% of those completed preventive treatment and 8% stopped preventive treatment due to adverse events. Two-thirds of the notified cases were detected through contact investigation.

Increasing numbers of persons with immunosuppressive disorders, elderly persons and foreign-born persons were notified in recent years, due to policy changes and the introduction of the interferon-γ release assay. Children (96%) and the immunosuppressed (95%) were more likely to start preventive treatment. Children (93%) were also more likely to complete preventive treatment, as were persons treated with rifampicin or rifampicin/isoniazid regimens (91% and 92%, respectively). The latter groups were also 40% less likely to stop preventive treatment due to adverse events.

Under these operational conditions, the estimated risk reduction on incident TB in the target population for LTBI management is 40–60%.

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Introduction

Background

In May 2014, the World Health Organization (WHO) launched the End TB Strategy to step up efforts for the elimination of tuberculosis (TB) worldwide [1]. For low-incidence countries, defined as countries with a TB incidence of less than 10 per 100 000 population, WHO and the European Respiratory Society (ERS) developed a Framework towards TB elimination [2, 3] and WHO developed guidelines for latent TB infection (LTBI) management in low TB burden countries [4]. One of the key interventions of the Framework is screening for LTBI in populations at high risk for TB and providing preventive treatment for those infected. The Netherlands already reached the status of a low TB incidence country in the early 1980s. Since then, TB notification rates have declined steadily to 4.9 per 100 000 persons in 2014; 73% of patients were foreign-born in 2014, and TB notification rates were 1.5 and 33.3 cases per 100 000 in the Dutch-born population and the foreign-born population, respectively.

Targeted LTBI screening of specific high-risk groups has been a pillar of TB control for decades in the Netherlands in addition to active TB case finding, such as radiological screening of new immigrants and asylum seekers [5] (table 1). Municipal Public Health Services (MPHSs) carry out LTBI screening and treatment among TB contacts, (health) professionals frequently exposed to TB and travellers to TB endemic areas. LTBI screening of target groups such as immunocompromised persons is mostly done in a clinical setting. The diagnosis of LTBI is based on 1) the tuberculin skin test (TST) or interferon-γ release assay (IGRA), 2) assessment of the likelihood of (recent) TB exposure and 3) exclusion of active TB. Screening algorithms differ between specific age and target groups (online supplementary table S1). IGRA was first used in the Netherlands around 2005. In 2010, the national guidelines for LTBI diagnosis recommended a two-step approach using IGRA in those with a TST reaction ⩾5 mm (online supplementary table S1) [6]. Persons diagnosed with LTBI are offered preventive treatment or 2 years of radiological follow-up, depending on their probability of developing TB, contra-indications for preventive treatment and willingness to start preventive treatment. Before 2000, the preferred preventive treatment regimen was 6 months of isoniazid. From 2000 onwards, shorter regimens were increasingly used and

TABLE 1 Major policy changes in latent tuberculosis (TB) infection (LTBI) diagnosis and treatment 1993–2013

Period (revision)	Policy (guideline)	Target group
1993–2004	Source and contact investigation	Close contacts, excluding persons born before 1945, immigrants from endemic areas[#], BCG-vaccinated persons
	Healthcare workers and other professional contacts of risk groups	Healthcare workers and other professional contacts of risk groups (such as staff asylum reception centres, prison staff), pre-exposure and periodic screening
	Travellers to TB endemic areas[#]	Long-term travellers (>3 months), pre- and post-exposure
	Pre-BCG examination	Children aged 6 months to 12 years with a parent from an endemic area (children aged 6–12 months only when travelled in endemic area)
2004	Preventive treatment of persons with inactive fibrotic lesions with no history of previous TB treatment	New immigrants arriving from TB endemic countries
2004	Screening before treatment with TNF-α inhibitors	Patients starting TNF-α inhibitor treatment
2005	Source and contact investigation	Expansion of eligibility for LTBI screening to persons vaccinated with BCG during infancy and immigrants having lived <12 years in TB endemic areas
2008	Screening HIV-infected persons	HIV-infected persons
2009	Introduction of short-course preventive treatment regimen with 3 months of rifampicin/isoniazid and 4 months of rifampicin (LTBI treatment guideline)	All persons eligible for preventive treatment
2010	IGRA officially included in diagnostic algorithm for LTBI	BCG-vaccinated persons, close TB contacts originating from TB endemic areas, persons born before 1945
2013	Travellers to TB endemic areas[#,¶]	Post-exposure for travellers with high risk of exposure to TB determined by: risk setting, length of stay and TB incidence

BCG: bacille Calmette–Guerin; TNF: tumour necrosis factor; IGRA: interferon-γ release assay. [#]: endemic area defined as estimated TB incidence according to the World Health Organization of more than 50 per 100 000 population; [¶]: pre-exposure examination of travellers was abolished and post-exposure screening only for specified high-risk travellers.

4 months of rifampicin only or 3 months of rifampicin/isoniazid has been recommended in national guidelines since 2008.

In this paper, we describe the LTBI recording and reporting tool, and the results of 21 years of LTBI monitoring and evaluation, focusing on trends in target groups for LTBI screening and preventive treatment regimens used. In addition, we examine the cause of death during preventive treatment, and explore risk factors associated with preventive treatment initiation, preventive treatment completion and preventive treatment discontinuation related to the occurrence of adverse events and estimated the risk reduction by preventive treatment for active TB among the population identified with LTBI.

LTBI monitoring system

The MPHSs register LTBI cases in the Netherlands Tuberculosis Register (NTR). The NTR is an anonymised nationwide web-based case-based surveillance system for TB and LTBI. TB notification is mandatory and LTBI is reported on a voluntary basis. The system started in 1993 as a paper case-based registry for both TB and LTBI cases. It captures LTBI cases newly diagnosed by or reported to the MPHSs. Data recorded include patients' demographic characteristics, target group, diagnostic method and patient management (preventive treatment regimen or radiological follow-up), completion of preventive treatment, and reason for interrupting preventive treatment (adverse events, development of active TB or nonadherence). Reasons for nonacceptance of preventive treatment are not captured. Data are collected in two stages: demographic and diagnostic data in stage 1, and treatment outcome data in stage 2. For each stage, dedicated data managers validate the data by checking for internal consistency and completeness. Only data with a validated stage 1 status are used to determine the number of cases reported and only treatment outcome results with a validated stage 2 status are used to determine the treatment outcome results.

In 2005, the case record form (CRF) for notification was split in separate CRFs for TB and LTBI. Both forms were integrated with the central web-based register for infectious disease surveillance "OSIRIS", hosted by the National Institute for Public Health and the Environment (RIVM). The content of the LTBI CRF was revised. At that time, it was observed that the case definition of LTBI to be reported was not clear: some MPHSs were only reporting cases starting preventive treatment, while others would also report newly diagnosed cases considered as "old or remote" infections not eligible for preventive treatment. A new case definition of LTBI was agreed, strictly based on the eligibility for preventive treatment according to the national guidelines. This includes cases with 1) a high likelihood of recent infection (<2 years ago), 2) severe immunosuppressive disorders (*e.g.* HIV infection), 3) pulmonary fibrotic lesions consistent with active TB in the past and without adequate treatment, and 4) planned immunosuppressive therapy (tumour necrosis factor (TNF)-α antagonists/organ transplantation). Child TB contacts and immunocompromised TB contacts receiving primary chemoprophylaxis are not considered as reportable LTBI cases. They are reported if they show a test conversion later.

Additional categories for target groups of LTBI screening which previously were recorded under "other" were introduced in the CRF: persons with severe immunosuppressive disorders or before use of immunosuppressive medication, persons with inactive intra-thoracic fibrotic lesions and IGRA as the diagnostic method. The nature of adverse events during preventive treatment was no longer recorded in the new CRF for LTBI. Both TB and LTBI data are analysed and reported annually in the national surveillance report and made available for use by interested parties through a publicly accessible website (www.tbc-online.nl/eng/).

Methods

The NTR registration committee approved the use of data from the NTR of all LTBI cases notified in the period 1993–2013 for the purpose of the study. In addition, we collected information from the MPHSs through a short questionnaire on the cause of death for patients who were reported to have died during preventive treatment.

We conducted a descriptive analysis of the population characteristics and trends in treatment acceptance and treatment completion over time. Trend analysis was stratified according to country of origin and target groups for LTBI management.

Target groups were classified reflecting the likelihood of recent exposure: contact investigation, post-exposure screening (screening of at-risk professionals and travellers), pre-exposure screening (at-risk professionals and travellers and pre-bacille Calmette–Guerin (BCG) vaccination) and screening related to immunosuppression/before immunosuppressive therapy. The latter group includes both immunocompromised persons and immunocompetent patients. For the purpose of the analyses, an adverse event was defined as any adverse event leading to discontinuation of preventive treatment.

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We conducted a multivariable analysis with logistic regression. We determined the factors independently associated with 1) treatment initiation, 2) treatment completion and 3) (discontinuation due to) adverse events with multivariable regression analysis. *A priori* confounders (age, sex, country of origin, period) were fixed in the multivariable model. Other variables yielding a p-value <0.2 in the univariable analysis were included in the model, and the most parsimonious model was selected by backward elimination guided by the change in log likelihood and coefficients of successive models. Statistical analysis was performed in SPSS version 22.0 (SPSS, Chicago, IL, USA).

The risk reduction of preventive treatment for active TB was calculated as the product of the rate of preventive treatment initiation and completion in the period 2009–2013 and the reported efficacy of the different preventive treatment regimens (60–90%) [7].

Results

Trends and characteristics of cases notified with LTBI

In total, 37729 persons were diagnosed and reported with LTBI from 1993–2013. The annual number of registered LTBI cases increased between 1993 and 1999 from 1356 to 2435 and dropped to the level of 1993 from 2010 onwards (figure 1). After 2005, the number decreased for cases starting treatment as well as for those not starting treatment. The number of reported Dutch-born LTBI cases increased until 2002, and then decreased steeply between 2005 and 2013 from 1870 to 690 cases, while the number of reported foreign-born LTBI cases increased from 271 (13%) to 655 (49%) in the same period. At the same time, the age (mean±SD) of those identified with LTBI increased from 27.3±10.1 years in 1993 to 37.0±16.2 years in 2013. After 2005, IGRA was increasingly used for the diagnosis of LTBI, up to 83% in the cases notified in 2013 (figure 1).

Preventive treatment initiation

In total, 28931 of 37729 (77%) reported LTBI cases started preventive treatment (figure 2). During 1993–2013, the percentage of persons with LTBI receiving preventive treatment dropped from 97% to 65% in 2005, steadily increased again to 79% in 2011 and dropped again to 71% in 2013. Overall, the main indication for LTBI screening among LTBI cases initiating preventive treatment was contact investigation (61%, annual range 54–71%), followed by pre-exposure evaluation (19%, annual range 7–28%). Until 2005, the number of LTBI cases initiating preventive treatment increased in all target groups. After 2005, the absolute number of cases declined in all target groups, except in the new target groups of persons with immunocompromised conditions and persons with fibrotic lesions.

Persons registered from 1993 to 1996 (93%), children <15 years (96%), immunocompromised persons (95%), persons with fibrotic lesions (83%) and persons identified through contact investigation (79%) were more likely to start preventive treatment. After multivariable adjustment, having received preventive treatment was associated with registration in the period 1993–1996 or 2009–2013, age <15 years, female sex, contact investigation, immune disorder or fibrotic lesions as reason for testing and negative BCG vaccination status. Being tested with IGRA alone was negatively associated with initiating preventive treatment (table 2).

Preventive treatment completion

In total, 27748 of 28931 persons (96%) initiated on preventive treatment had a registered and validated result of preventive treatment. In addition to the 1183 cases on preventive treatment without a validated registered result of preventive treatment, 2192 persons with a validated result were lost to follow-up, *i.e.* a total of 12% of those initiated on preventive treatment.

Of 27748 persons with a valid result of preventive treatment, 85% completed the treatment, *i.e.* 82% of the total registered cases on preventive treatment. Children (93%), professionals (91%), travellers post-exposure (93%), and persons with fibrotic lesions (93%) were more likely to complete the treatment. The completion rates varied over time. After the multivariable analysis, diagnosis in 1993–1996 or 2009–2013, age <15 years, male sex, Dutch born, rural residence, target groups immunosuppression, professional at-risk, traveller and fibrotic lesions, and rifampicin-containing regimens were associated with treatment completion (table 3). Compared with persons treated with 6–9 months of isoniazid, the adjusted odds ratios for completing preventive treatment for persons treated with 4 months of rifampicin or a combination of 3–4 months of rifampicin/isoniazid were 1.7 (95% CI 1.3–2.2) and 1.7 (95% CI 1.4–2.0), respectively.

Adverse events

In total, 2105 (7.6%) persons discontinued preventive treatment because of adverse effects. The nature of adverse events was only registered during the period 1993–2004. Of 1392 persons who stopped preventive treatment during this period due to adverse events, 33% had hepatic dysfunction, 10% neurological dysfunction, 11% psychological dysfunction, 10% allergy, 1% visual dysfunction, 1% arthralgia, 21% nonspecified adverse events and 12% unknown.

17 (0.1%) persons were reported to have died during preventive treatment. For seven of these, of whom five registered before 2005, we were unable to retrieve information on the cause of death. For the remaining 10, the cause of death was not related to the preventive treatment according to the MPHSs. Two persons committed suicide with an overdose of isoniazid and eight persons died from cardiac events, malignancies or other specified nonpreventive treatment-related causes.

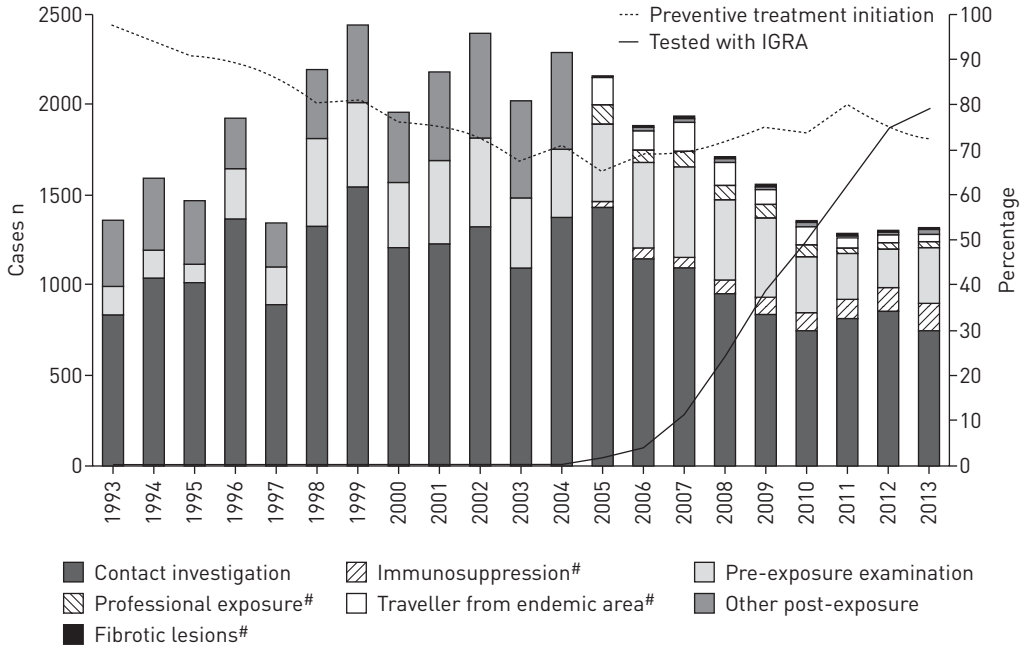

FIGURE 1 Number of cases with latent tuberculosis infection by target group for screening, and percentage screened with interferon-γ release assay (IGRA) and preventive treatment initiation (1993–2013). #: reported since 2005.

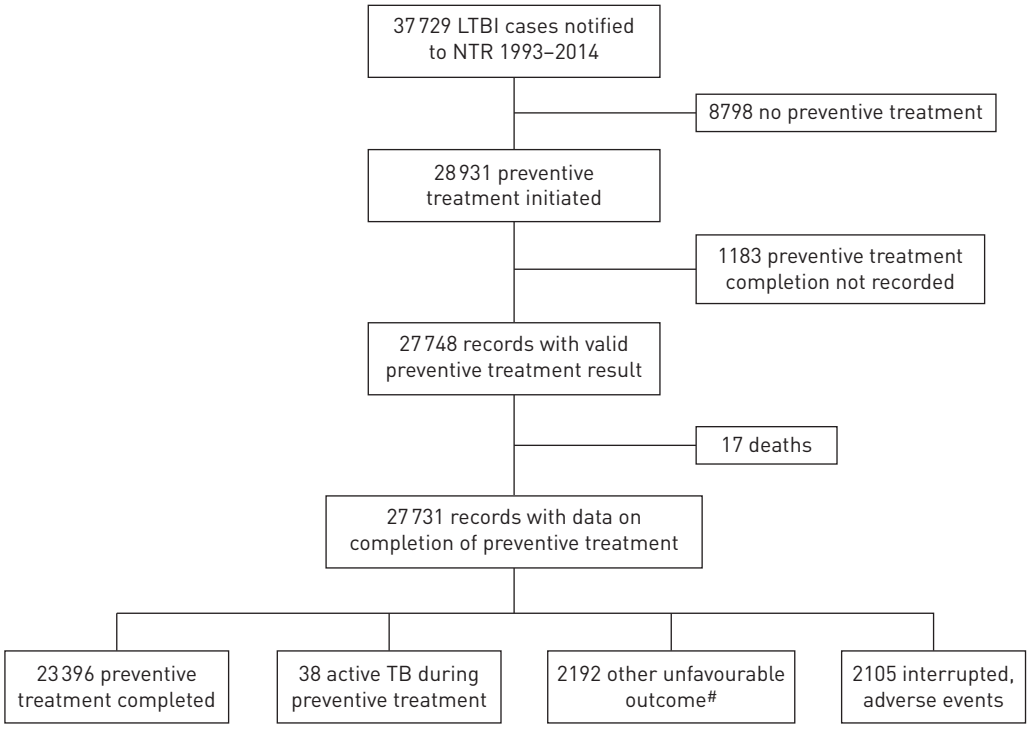

FIGURE 2 Flowchart for risk factor analysis in latent tuberculosis (TB) infection (LTBI). NTR: Netherlands Tuberculosis Register. #: other unfavourable outcome is defined as treatment interrupted by patient, transfer out or outcome unknown.

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TABLE 2 Univariable and multivariable analysis of determinants of preventive treatment initiation in persons notified with latent tuberculosis (TB) infection initiated on preventive treatment

	Preventive treatment initiation		Univariable		Multivariable	
	No	Yes[#]	OR (95% CI)	p-value	aOR (95% CI)	p-value
Total	8798	28 931 (77)				
Period						
1993–1996	473	5860 (93)	4.3 (3.8–4.8)	<0.001	1.9 (1.3–3.1)	0.002
1997–2000	1548	6370 (80)	1.4 (1.3–1.5)	<0.001	0.69 (0.45–1.6)	0.09
2001–2004	2541	6352 (71)	0.87 (0.80–0.93)	<0.001	0.45 (0.29–0.69)	<0.001
2005–2008	2471	5235 (68)	0.73 (0.68–0.79)	<0.001	0.65 (0.59–0.72)	<0.001
2009–2013	1765	5114 (74)	1.0		1.0	
Age group years						
0–14	148	3153 (96)	1.0		1.0	
15–24	1677	8891 (84)	0.25 (0.21–0.30)	<0.001	0.26 (0.22–0.31)	<0.001
25–34	1811	7207 (80)	0.19 (0.16–0.22)	<0.001	0.18 (0.15–0.21)	<0.001
35–44	1921	5292 (73)	0.13 (0.11–0.15)	<0.001	0.11 (0.10–0.14)	<0.001
45–54	2232	3250 (59)	0.07 (0.06–0.08)	<0.001	0.06 (0.05–0.07)	<0.001
55–64	884	906 (51)	0.05 (0.04–0.06)	<0.001	0.04 (0.04–0.05)	<0.001
⩾65	125	232 (65)	0.09 (0.07–0.11)	<0.001	0.05 (0.03–0.06)	<0.001
Sex						
Male	4506	14 222 (76)	1.0		1.0	
Female	4289	14 688 (77)	1.1 (1.0–1.1)	0.001	1.1 (1.0–1.1)	0.002
Residence						
Urban	1806	6478 (78)	1.0			
Rural	6992	22 453 (76)	0.90 (0.84–0.95)	<0.001		
Origin						
Foreign born	1579	4659 (75)	1.0		1.0	
Dutch born	7131	24 057 (77)	1.1 (1.1–1.2)	<0.001	1.1 (0.98–1.2)	0.11
Unknown	88	215 (71)	0.82 (0.63–1.1)	0.12	0.75 (0.56–1.0)	0.05
BCG vaccination						
No BCG	6990	24 785 (78)	1.0	<0.001	1.0	
BCG	1050	2575 (71)	0.69 (0.64–0.75)	<0.001	0.79 (0.71–0.88)	<0.001
Unknown	758	1571 (67)	0.58 (0.53–0.64)	<0.001	0.66 (0.60–0.74)	<0.001
Diagnostic test						
TST	2792	6762 (71)	1.0		1.0	<0.001
IGRA	256	453 (64)	0.73 (0.62–0.86)	<0.001	0.79 (0.65–0.96)	0.02
TST and IGRA	1169	2998 (72)	1.1 (0.98–1.2)	0.16	1.1 (0.98–1.2)	0.10
Unknown	4581	18 718 (80)	1.7 (1.6–1.8)	<0.001	1.7 (1.1–2.6)	0.02
Target group						
TB contact	4705	18 214 (79)	1.0	<0.001	1.0	<0.001
Immunosuppression	42	779 (95)	4.8 (3.5–6.5)	<0.001	13.8 (9.9–19.1)	<0.001
Pre-exposure examination	2252	5014 (69)	0.58 (0.54–0.61)	<0.001	0.49 (0.46–0.52)	<0.001
Professional at risk[¶]	220	391 (64)	0.46 (0.39–0.54)	<0.001	0.62 (0.51–0.74)	<0.001
Traveller[¶]	258	563 (69)	0.56 (0.48–0.66)	<0.001	0.55 (0.46–0.65)	<0.001
Other post-exposure	1297	3856 (75)	0.77 (0.72–0.82)	<0.001	0.53 (0.49–0.57)	<0.001
Fibrotic lesions	24	114 (83)	1.2 (0.79–1.9)	0.36	2.1 (1.3–3.4)	0.002

Data are presented as n or n (%), unless otherwise stated. OR: odds ratio; aOR: adjusted OR; BCG: bacille Calmette–Guerin; TST: tuberculin skin test; IGRA: interferon-γ release assay. [#]: percentage treatment initiated of row total given in parentheses; [¶]: post-exposure.

Factors associated with interruption of treatment due to adverse events were female sex, Dutch born, rural residence and isoniazid monotherapy as preventive treatment regimen. Diagnosis from 1997 to 2008, age <5 years and rifampicin-containing regimens were associated with a lower likelihood of interruption of treatment due to adverse events (table 4). After controlling for these factors and compared with persons treated with 6–9 months of isoniazid, the adjusted odds ratio of stopping preventive treatment due to adverse events was lowest among persons treated with 4 months of rifampicin and 3–4 months of rifampicin/isoniazid: 0.63 (95% CI 0.44–0.90) and 0.58 (95% CI 0.45–0.74), respectively.

Risk reduction for developing TB in those found with LTBI

In the period 2009–2013, 74% of eligible persons started preventive treatment and 90% completed preventive treatment. Assuming an estimated effectiveness of preventive treatment regimens between 60%

TABLE 3 Factors associated with completion of preventive treatment

	Preventive treatment completion		Univariable		Multivariable	
	No	Yes[#]	OR (95% CI)	p-value	aOR (95% CI)	p-value
Total	4097	23 634 (85)				
Period						
1993–1996	718	4812 (87)	0.77 (0.68–0.87)	<0.001	1.0 (0.86–1.2)	0.84
1997–2000	1019	5080 (83)	0.57 (0.51–0.64)	<0.001	0.77 (0.65–0.90)	0.001
2001–2004	1075	4898 (82)	0.52 (0.47–0.59)	<0.001	0.74 (0.63–0.87)	<0.001
2005–2008	776	4420 (85)	0.66 (0.58–0.74)	<0.001	0.79 (0.67–0.92)	0.002
2009–2013	509	4424 (90)	1.0			1.0
Age group years						
0–14	222	2858 (93)	1.0			1.0
15–24	1075	7471 (87)	0.54 (0.46–0.63)	<0.001	0.53 (0.45–0.61)	<0.001
25–34	1068	5817 (84)	0.42 (0.36–0.49)	<0.001	0.40 (0.35–0.47)	<0.001
35–44	927	4129 (82)	0.35 (0.30–0.40)	<0.001	0.33 (0.28–0.39)	<0.001
45–54	630	2461 (80)	0.30 (0.26–0.36)	<0.001	0.28 (0.24–0.33)	<0.001
55–64	143	717 (83)	0.39 (0.31–0.49)	<0.001	0.30 (0.24–0.38)	<0.001
⩾65	32	181 (85)	0.44 (0.29–0.66)	<0.001	0.31 (0.20–0.47)	<0.001
Sex						
Male	1956	11 634 (86)	1.0			1.0
Female	2139	11 981 (85)	0.94 (0.88–1.0)	0.07	0.93 (0.87–0.99)	0.03
Origin						
Foreign born	656	3817 (85)	1.0	0.83		1.0
Dutch born	3408	19 646 (85)	0.99 (0.90–1.1)	0.81	1.2 (1.0–1.3)	0.01
Unknown	33	171 (84)	0.89 (0.61–1.3)	0.55	1.0 (0.70–1.5)	0.84
Residence						
Urban	981	5393 (85)	1.0			1.0
Rural	3116	18 241 (85)	1.1 (0.99–1.2)	0.11	1.1 (1.0–1.2)	0.05
BCG vaccination						
No BCG	3559	20 226 (85)	1.0	0.04		
BCG	326	2162 (87)	1.2 (1.0–1.3)	0.01		
Unknown	212	1246 (85)	1.0 (0.89–1.2)	0.62		
Diagnostic test						
TST	894	5788 (87)	1.0			
IGRA	54	368 (87)	1.1 (0.78–1.4)	0.73		
TST and IGRA	315	2582 (89)	1.3 (1.1–1.5)	0.001		
Unknown	2834	14 896 (84)	0.81 (0.75–0.88)	<0.001		
Target group						
TB contact	2588	14 972 (85)	1.0			1.0
Immunosuppression	92	628 (87)	1.2 (0.94–1.5)	0.15	1.5 (1.2–1.9)	0.001
Pre-exposure examination	691	4140 (86)	1.0 (0.95–1.1)	0.45	1.0 (0.92–1.1)	0.87
Professional at risk[¶]	36	348 (91)	1.7 (1.2–2.4)	0.004	1.6 (1.1–2.2)	0.01
Traveller[¶]	41	511 (93)	2.2 (1.6–3.0)	<0.001	1.79 (1.3–2.5)	<0.001
Other post-exposure	641	2933 (82)	0.79 (0.72–0.87)	<0.001	0.83 (0.75–0.92)	<0.001
Fibrotic lesions	8	102 (93)	2.2 (1.1–4.5	0.03	4.4 (2.1–9.2)	<0.001
Preventive treatment regimen						
6–9 months isoniazid	3418	19 423 (85)	1.0			1.0
4 months rifampicin	65	667 (91)	1.8 (1.4–2.3)	<0.001	1.7 (1.3–2.2)	<0.001
3–4 months rifampicin/isoniazid	269	2896 (92)	1.9 (1.7–2.2)	<0.001	1.7 (1.4–2.0)	<0.001
Other or unknown	345	648 (65)	0.33 (0.29–0.38)	<0.001	0.35 (0.30–0.40)	<0.001

Data are presented as n or n (%), unless otherwise stated. OR: odds ratio; aOR: adjusted OR; BCG: bacille Calmette–Guerin; TST: tuberculin skin test; IGRA: interferon-γ release assay; TB: tuberculosis. [#]: percentage completed of row total given in parentheses; [¶]: post-exposure.

and 90%, the risk reduction of preventive treatment for active TB among the total population identified with LTBI is between 40% and 60%.

Discussion

During 21 years of programmatic LTBI management in the Netherlands, 37 729 persons were registered with LTBI; of those, 77% started preventive treatment. In total, 82% of all reported cases on treatment were known to have completed the treatment. Two-thirds of the notified LTBI cases were detected through contact

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TABLE 4 Factors associated with discontinuing treatment due to adverse events

	Stopped due to adverse events		Univariable		Multivariable	
	No	Yes[#]	OR (95% CI)	p-value	aOR (95% CI)	p-value
Total	25 626	2105 (7.6)				
Period						
1993–1996	5198	332 (6.0)	1.0			1.0
1997–2000	5593	506 (8.3)	1.4 (1.2–1.6)	<0.001	1.4 (1.2–1.4)	<0.001
2001–2004	5419	554 (9.3)	1.6 (1.4–1.8)	<0.001	1.6 (1.3–1.8)	<0.001
2005–2008	4735	461 (8.9)	1.5 (1.3–1.8)	<0.001	1.5 (1.3–1.8)	<0.001
2009–2013	4681	252 (5.1)	0.84 (0.71–1.00)	0.05	1.1 (0.90–1.4)	0.29
Age group years						
0–14	3042	38 (1.2)	1.0			1.0
15–24	8127	419 (4.9)	4.1 (3.0–5.8)	<0.001	3.7 (2.6–5.2)	<0.001
25–34	6359	526 (7.6)	6.6 (4.7–9.2)	<0.001	6.6 (4.7–9.2)	<0.001
35–44	4508	548 (10.8)	9.7 (7.0–13.5)	<0.001	9.9 (7.1–13.8)	<0.001
45–54	2649	442 (14.3)	13.4 (9.6–18.7)	<0.001	14.0 (10.0–19.6)	<0.001
55–64	750	110 (12.8)	11.7 (8.0–17.1)	<0.001	15.5 (10.5–22.7)	<0.001
⩾65	191	22 (10.3)	9.0 (5.2–15.5)	<0.001	14.4 (8.1–25.6)	<0.001
Sex						
Male	12 781	809 (6.0)	1.0			1.0
Female	12 824	1296 (9.2)	1.6 (1.5–1.8)	<0.001	1.7 (1.6–1.9)	<0.001
Origin						
Foreign born	4297	176 (3.9)	1.0			1.0
Dutch born	21 136	1918 (8.3)	2.2 (1.9–2.6)	<0.001	1.8 (1.5–2.1)	<0.001
Unknown	193	11 (5.4)	1.4 (0.75–2.6)	0.29	1.3 (0.67–2.4)	0.46
Residence						
Urban	6025	349 (5.5)	1.0			1.0
Rural	19 601	1756 (8.2)	1.5 (1.4–1.7)	<0.001	1.3 (1.2–1.5)	<0.001
Target group						
TB contact	16 192	1368 (7.8)	1.0			1.0
Immunosuppression	669	51 (7.1)	0.90 (0.67–1.2)	0.46	0.57 (0.41–0.79)	<0.001
Pre-exposure examination	4469	362 (7.5)	0.96 (0.85–1.1)	0.49	1.0 (0.90–1.2)	0.80
Professional at risk[¶]	356	28 (7.3)	0.93 (0.63–1.4)	0.72	0.87 (0.58–1.3)	0.48
Traveller[¶]	525	27 (4.9)	0.61 (0.41–0.90)	0.01	0.75 (0.50–1.1)	0.16
Other post-exposure	3309	265 (7.4)	0.94 (0.82–1.1)	0.41	1.1 (0.91–1.2)	0.50
Fibrotic lesions	106	4 (3.6)	0.45 (0.16–1.2)	0.11	0.62 (0.22–1.7)	0.36
Preventive treatment regimen						
6–9 months isoniazid	20 991	1850 (8.1)	1.0			1.0
4 months rifampicin	694	38 (5.2)	0.62 (0.45–087)	0.005	0.63 (0.44–0.90)	0.01
3–4 months rifampicin/isoniazid	2818	122 (4.1)	0.49 (0.41–0.59)	<0.001	0.58 (0.45–0.74)	<0.001
Other or unknown	1123	95 (8.5)	1.1 (0.89–1.4)	0.33	0.93 (0.74–1.2)	0.56

Data are presented as n or n (%), unless otherwise stated. OR: odds ratio; aOR: adjusted OR; TB: tuberculosis. [#]: percentage stopped of row total given in parentheses; [¶]: post-exposure.

investigation. Target groups and demographic characteristics of cases changed over time, with more cases with immunosuppressive disorders, older cases and foreign-born cases notified in the last decade. Preventive treatment initiation was highest in groups more likely to progress to active TB: immunosuppressed persons, children and TB contacts. Children and immunosuppressed persons were also more likely to complete preventive treatment, as were persons treated with the rifampicin or rifampicin/isoniazid regimens. Those treated with these regimens were also less likely to stop preventive treatment due to adverse events.

The policy changes over time influenced annual rates of preventive treatment initiation and completion in various ways. Expansion of LTBI screening to older age and foreign-born groups reduced preventive treatment acceptance and preventive treatment completion, but the overall rates were likely mitigated by the introduction of immunosuppressed persons as a target group that showed relatively high rates of preventive treatment acceptance and completion.

The short-course treatment regimens of 3–4 months of rifampicin/isoniazid and 4 months of rifampicin were rapidly adopted since introduction in the Netherlands in 2009. The relatively high treatment completion rates are comparable to those reported among close contacts [8]. A recent systematic review of

randomised clinical trials showed similar effectiveness and significantly less adverse events of rifampicin monotherapy and of the rifapentine/isoniazid regimen compared with isoniazid monotherapy [9]. In this study, the occurrence of adverse events for 3–4 months of rifampicin/isoniazid was not significantly different from those treated with isoniazid monotherapy, but the evidence used in this review was rated as very weak. In our observational study more persons receiving 6–9 months of isoniazid discontinued treatment because of adverse events. We conclude that in the Dutch setting, until the 12-dose rifapentine/isoniazid regimen becomes available, the other rifamycin-based regimens have better completion rates and are thus to be preferred over the regimens with isoniazid alone.

Our study has a number of limitations. Registration is not mandatory, and in the course of the 21 years covered eligible LTBI cases for reporting have been both under-and overreported for the reasons explained above. Trends in preventive treatment initiation are therefore difficult to interpret. However, since 2005 the data have been used increasingly for management information purposes as well as surveillance, which may have improved accuracy, comparability and completeness. Therefore, we believe the treatment initiation rate over the period 2009–2013 is a reasonable reflection of the actual situation in the public health sector. Cases diagnosed and managed in the clinical sector, such as candidates for anti-TNF-α treatment, are increasingly reported since MPHSs have intensified collaboration with clinicians and provide treatment support to LTBI patients as well as TB patients identified in the clinical sector.

Another limitation when describing trends in preventive treatment initiation is the heterogeneity of the study population caused by policy changes over the years. For instance, until 2005, BCG-vaccinated persons and persons from high endemic areas or born in the Netherlands before 1945 (those with a high likelihood of remote infection) were not targeted for LTBI screening, not even in the context of contact investigation. Following the introduction of IGRA and the European consensus statement for contact investigation in 2010 [10], close contacts of infectious TB patients were included as a target group for LTBI testing irrespective of age, BCG vaccination status or country of origin. Some MPHSs were quick to adopt the new guidelines and others took longer. Such differences are difficult to avoid, because public health in the Netherlands is the responsibility of the local authority. Evidence-based and best-practice guidelines have been developed by the Committee for Practical TB Control Netherlands (CPT) on a consensus basis for more than 60 years, but the CPT has no mandate to demand full implementation.

The Netherlands is one of the few European countries monitoring and evaluating programmatic LTBI management [11]. A particular strength of the Dutch LTBI register is that it is integrated with the web-based TB surveillance system, which has a long-standing reputation for completeness and reliability [12]. However, to enable the evaluation of programmatic LTBI management, the present system needs adjustments so as to properly distinguish clinical target groups, reasons for not initiating preventive treatment, and the occurrence and nature of adverse events. Furthermore, the system does not record chemoprophylaxis for vulnerable populations (child TB contacts and immunocompromised TB contacts). This is an important intervention to prevent (serious) TB in these groups, which requires monitoring and evaluation as well. A revision of the CRF encompassing the variables listed above is planned for 2016.

The estimated risk reduction of preventive treatment for active TB among the population identified with LTBI was between 40% and 60%. However, a high rate of acceptance and coverage of LTBI screening in the eligible target groups is also required for optimal impact of programmatic LTBI management. Information about the denominator of the target groups for LTBI and the number of persons per target group screened for LTBI have to be retrieved from other, generally not readily available sources. For TB contacts in the Netherlands, the information has been available through the TB register since 2006. For each notified TB patient it records whether a contact investigation was performed, how many contacts were eligible for screening, how many were screened and how many were identified with TB or LTBI [13]. In the period 2006–2010, 87% of contacts eligible for screening were screened for TB, 73% were screened for LTBI and of those, 7% tested positive for LTBI [14].

Conclusion

The WHO End TB strategy calls upon low TB burden countries to move towards TB elimination by targeting high-risk TB groups for LTBI screening and preventive treatment [4]. The example of the Netherlands shows that given the right infrastructure and organisation of services, such groups can be successfully reached and served. Committed to the WHO End TB objective of 50% reduction of TB incidence by 2035, the Netherlands is ready to face the next challenge and explore the feasibility of targeting new migrants from high TB endemic countries for LTBI screening and preventive treatment in the coming years. Our study shows that when a high coverage and treatment acceptance can be achieved, a reduction of incident TB cases of 40–60% among new migrants is feasible. A flexible and sound TB surveillance system incorporating LTBI management is key to providing the basic indicators required for evaluation.

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