Risk of developing tuberculosis disease among persons diagnosed with latent tuberculosis infection in the Netherlands

Connie G.M. Erkens[1], Erika Slump[2], Maurits Verhagen[3], Henrieke Schimmel[2], Frank Cobelens[1,4,5] and Susan van den Hof[1,4,5]

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]Public Health Service (GGD) Limburg-Noord, Roermond, The Netherlands. [4]Dept of Global Health, Academic Medical Center, Amsterdam, The Netherlands. [5]Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands.

Correspondence: Connie G.M. Erkens, KNCV Tuberculosis Foundation, PO Box 146, Den Haag, Zuid-Holland 2501CC, The Netherlands. E-mail: connie.erkens@kncvtbc.org

ABSTRACT Diagnosis and preventive treatment of latent tuberculosis infection (LTBI) among high-risk groups is recommended to achieve tuberculosis (TB) elimination in low-incidence countries.

We studied TB incidence rates among those notified with LTBI in the Netherlands from 2005 to 2013 and analysed associated risk factors. We stratified analyses by target group for screening, and by initiation and completion of preventive treatment.

The incidence for those completing, stopping and not receiving preventive treatment was 187, 436 and 355 per 100 000 person-years for contacts of TB patients, respectively, and 63, 96 and 110 per 100 000 person-years for other target groups. The rate ratio for TB development among contacts compared to other target groups was 3.1 (95% CI 2.0–4.9). In both groups, incidence was highest in the first year after diagnosis. Independent factors associated with progression to TB among contacts were age <5 years and stopping preventive treatment within 28 days compared to those not receiving preventive treatment. Among other target groups, being foreign born was the only risk factor associated with the risk of developing TB.

We conclude that the epidemiological impact of preventive treatment is highest in contacts of TB patients and limited in other target groups for LTBI management in the Netherlands.

@ERSpublications
Comparison of the impact of preventive treatment for latent tuberculosis in various target groups http://ow.ly/pSIG303vFSb

This article has supplementary material available from erj.ersjournals.com

Received: June 21 2016 | Accepted after revision: Aug 12 2016 | First published online: Oct 6 2016

Conflict of interest: None declared.

Introduction

The World Health Organisation [1] aims to step up efforts to eliminate tuberculosis (TB) worldwide and developed, in cooperation with the European Respiratory Society, a framework towards TB elimination [2]. A key intervention area for moving towards TB elimination in countries with a TB incidence of <10 per 100 000 population is screening and treatment for latent tuberculosis infection (LTBI) in high-risk groups [3].

In 2015, the TB incidence in the Netherlands was 5.1 per 100 000 population. Like in most low-incidence countries, the TB epidemiology is characterised by a low rate of transmission in the general population, occasional outbreaks, most cases of active TB being due to reactivation of LTBI, concentration of the disease in high-risk groups and challenges posed by cross-border migration [2]. Prevention of TB through detection and management of LTBI has been a pillar of TB control executed by the Municipal Public Health Centers (MPHCs) since the 1980s. The diagnosis of LTBI is based on the result of the tuberculin skin test (TST); since 2010, interferon-γ release assays (IGRAs) have been performed as a confirmatory test after the TST. Target groups for LTBI screening and preventive treatment (PT) originally included persons with a perceived high risk of recent TB infection, such as contacts of infectious TB patients (TB contacts), healthcare workers and other professionals in contact with high-risk groups for TB, and travellers to highly endemic areas. In the last decade, persons with a high likelihood of developing TB when infected, such as persons with inactive fibrotic lesions or compromised immunity, were included in the target group [4]. Persons diagnosed with LTBI are offered either 6–9 months of isoniazid, 4 months of rifampicin or a combination of rifampicin and isoniazid for a period of 3 months. Persons with contraindications for PT or who are unwilling to start PT are offered 2 years of radiological follow-up. The MPHCs notify all newly identified LTBI cases eligible for preventive treatment to the Netherlands Tuberculosis Register (NTR) on a voluntary basis [4]. In the period 1993–2014, 37 729 persons were notified with LTBI, of whom 77% started PT, of whom 82% completed the course [4]. These indicators show a reasonably good performance of the programme, but the impact of the intervention on the epidemiology of TB in the different target groups is more difficult to discern. Evaluations of actual impact of programmatic LTBI management have been performed through retrospective cohort studies among TB contacts [5–7], and randomised clinical trials among persons living with HIV [8, 9], or persons with silicosis [10] or fibrotic lesions [11]. In this study, we aimed to determine the TB risk reduction associated with PT among persons identified with LTBI in the Netherlands, and compare the risk between TB contacts and other target groups.

Methods

Data source and study population

We obtained the permission of the registration committee of the NTR to use and match data from the nationwide electronic surveillance system on all LTBI and TB records notified in the period 2005–2013. According to Dutch legislation (http://wetten.overheid.nl/BWBR0007021/2006-02-01), ethical approval is not required for the use of retrospectively collected and anonymised data. The case definition of LTBI notifiable to the NTR includes cases with: 1) a high likelihood of recent infection, *i.e.* <2 years ago; 2) pulmonary fibrotic lesions consistent with active TB in the past and without a history of adequate treatment; and 3) those with immunosuppression (HIV infection, other severe immunosuppressive disorders, planned tumour necrosis factor-α antagonist treatment or planned organ transplantation). Data recorded include patients' demographic characteristics, reason for LTBI examination, LTBI diagnostic method (TST with/without IGRA), patient management (PT or radiological follow-up). In cases where PT is initiated, completion of PT and reason for stopping PT (including the occurrence of adverse events or diagnosis of active TB) is recorded.

Statistical analyses

LTBI cases with validated PT outcome data and those who were radiologically followed up in the period 2005–2013 were included in the study population. Persons who reportedly had left the country to continue LTBI treatment outside the Netherlands (transfer out) or without information on LTBI treatment completion were excluded (figure 1). The LTBI records were matched with TB records notified to the NTR in the period 2005–2013 through either the LTBI-registration number or the combination of date of birth, sex, postal code and country of birth. Persons with a TB diagnosis within 28 days after LTBI diagnosis were excluded from the analysis, to rule out initial misclassification of TB diagnosis.

We calculated the TB incidence and rate ratios with corresponding 95% confidence intervals for the cohort notified with LTBI and eligible for PT, stratified by TB contacts and other target groups for LTBI screening. We calculated TB incidences for four periods of follow-up: 28 days to 1 year, 1–2 years, 2–5 years and ⩾5 years after the date of LTBI diagnosis. To correct for possible underdiagnosis of prevalent TB at initiation of PT, we performed a sensitivity analysis to calculate the effect of PT on incidence in the first year if cases who developed TB within 100 days after LTBI diagnosis would be excluded. For those persons

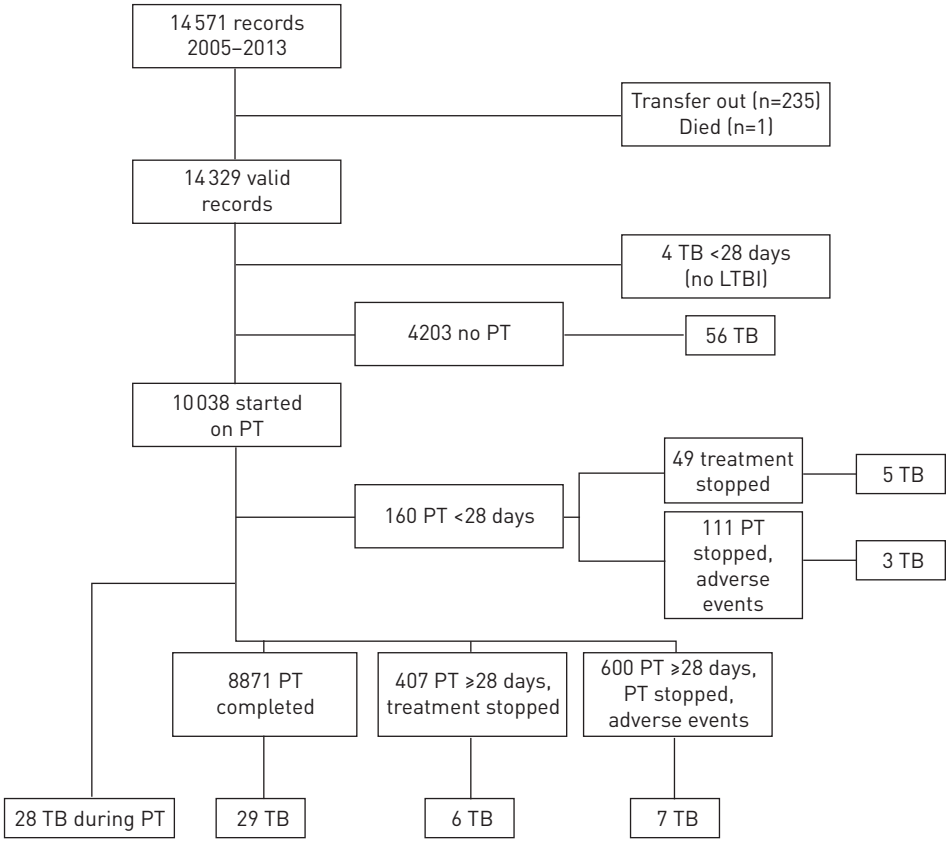

FIGURE 1 Study population: persons notified to Netherlands tuberculosis (TB) register with latent tuberculosis infection (LTBI). PT: preventive treatment.

diagnosed with TB during follow-up after LTBI diagnosis, person-years at risk (pyr) were calculated from the date of LTBI diagnosis until the date of TB diagnosis. For all other persons, we calculated pyr as the number of days between the date of LTBI diagnosis and the censor date March 1, 2014, assuming all cases survived to this date and were still present in the country. We used Cox regression analysis to identify person- and treatment-related characteristics associated with progression to active TB ⩾28 days after LTBI diagnosis for the total population, and stratified for TB contacts and other target groups. We also performed a sensitivity analysis assessing risk factors for progression to culture-positive TB only. Variables yielding a p-value <0.2 in univariate analysis were included in the multivariate regression analysis, 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 in SPSS 22.0 (IBM Analytics, Chicago, IL, USA).

Results

In total 134 of 14 241 records of LTBI cases in the study population matched with TB patients notified to the NTR with a date of diagnosis ⩾28 days after LTBI diagnosis (figure 1 and online supplementary material). The total number of pyr until the TB diagnosis of the censor date was 73 608, with a median of 5.5 years (interquartile range 3.0–7.4 years). The percentage of the LTBI cohort with a follow-up duration period <1, 1–2, 2–5 and ⩾5 years was 8%, 8%, 29% and 55%, respectively. 60% of the study population were TB contacts, 34% were healthcare workers or travellers (23% screened pre-exposure and 11% screened post-exposure), 5% were immunocompromised and 1% had fibrotic lesions (online supplementary material). The distribution of age groups from 0–4, 5–24, 25–44 and ⩾45 years was 2%, 31%, 38% and 29%, respectively, among all notified cases, 3%, 26%, 40% and 32% among TB contacts, and 1%, 38%, 36% and 25% among other target groups.

Characteristics of the 134 cases who developed TB are described in table 1. 76 (58%) cases had culture-confirmed TB disease. Of all TB cases, 63% developed disease within 1 year after LTBI diagnosis, 14% after 1–2 years, 18% after 2–5 years and 5% after an interval of ⩾5 years. 51% of the cases had pulmonary TB. Of 76 with culture-positive isolates, five had resistance to isoniazid, and four to isoniazid and rifampicin, of whom three and two persons, respectively, did not receive PT. The proportion of TB

 DOI: 10.1183/13993003.01157-2016

TABLE 1 Characteristics of cases developing tuberculosis (TB) after diagnosis of latent tuberculosis infection (LTBI), 2015–2013

	PT completed	PT stopped	No PT	Total
Total LTBI notified[#]	8871 (62%)	1167 (8%)	4203 (30%)	14241 (100%)
Total TB cases[#]	57 (43%)	21 (16%)	56 (42%)	134 (100%)
Interval between LTBI and TB diagnosis years[¶]				
Mean (median)	1.33 (0.45)	1.88 (0.92)	1.38 (0.88)	1.44 (0.77)
Range	0.08–7.27	0.12–6.55	0.10–7.01	0.08–7.27
Interquartile range	0.15–1.82	0.56–2.74	0.42–1.66	0.29–1.77
28 days to 1 year	38 (67%)	12 (57%)	34 (61%)	84 (63%)
1–2 years	5 (9%)	3 (14%)	11 (20%)	19 (14%)
2–5 years	12 (21%)	4 (19%)	8 (14%)	24 (18%)
⩾5 years	2 (4%)	2 (10%)	3 (5%)	7 (5%)
Age group[¶]				
0–4 years	6 (11%)	1 (5%)	1 (2%)	8 (6%)
5–34 years	36 (63%)	9 (43%)	23 (41%)	68 (51%)
35–54 years	13 (23%)	9 (43%)	25 (45%)	47 (35%)
⩾55 years	2 (4%)	2 (10%)	7 (13%)	11 (8%)
Reason for TB examination[¶]				
Presenting with TB symptoms	30 (53%)	9 (43%)	21 (38%)	60 (45%)
Contact investigation	20 (35%)	3 (14%)	8 (14%)	31 (23%)
Screening TB risk group[+]	4 (7%)	1 (5%)	21 (38%)	32 (24%)
Post-exposure screening of travellers and healthcare workers	1 (2%)	0 (0%)	1 (2%)	2 (1%)
Radiological screening in LTBI[§]	3 (5%)	6 (29%)	19 (34%)	28 (21%)
Other or unspecified	2 (4%)	2 (10%)	5 (9%)	9 (7%)
Diagnosis[¶]				
Pulmonary TB	31 (54%)	17 (81%)	46 (82%)	94 (70%)
Primary TB infection[f]	12 (21%)	0 (0%)	4 (7%)	16 (12%)
Other extrapulmonary TB	14 (25%)	4 (19%)	6 (11%)	24 (18%)
Microscopy result[¶]				
Sputum positive	7 (12%)	4 (19%)	8 (14%)	19 (14%)
Bronchoalveolar lavage positive	2 (4%)	3 (14%)	3 (5%)	8 (6%)
Negative	14 (25%)	8 (38%)	29 (52%)	51 (38%)
Unknown/not performed	34 (60%)	6 (29%)	16 (29%)	56 (42%)
Culture[¶]				
Positive	27 (47%)	13 (62%)	36 (64%)	76 (57%)
Negative	8 (14%)	5 (24%)	8 (14%)	21 (16%)
Unknown/not done	22 (39%)	3 (14%)	12 (21%)	37 (28%)
Drug resistance[##]				
Pan-sensitive	24 (89%)	12 (92%)	31 (86%)	67 (88%)
Isoniazid resistant	1 (4%)	1 (8%)	3 (8%)	5 (7%)
MDR	2 (7%)	0 (0%)	2 (6%)	4 (6%)
DNA fingerprint[¶]				
Cluster[¶¶]	23 (40%)	10 (48%)	32 (57%)	65 (49%)
Unique[++]	4 (7%)	3 (14%)	4 (7%)	11 (8%)
Culture negative or unknown	30 (53%)	8 (38%)	20 (36%)	58 (43%)
Comorbidity[¶]				
No comorbidity	33 (58%)	14 (67%)	32 (57%)	79 (59%)
Comorbidity[§§]	5 (9%)	4 (19%)	7 (13%)	16 (12%)
Unknown	12 (21%)	3 (14%)	17 (30%)	32 (24%)
TB treatment outcome[¶]				
Completed	53 (93%)	19 (90%)	52 (93%)	124 (93%)
Stopped	1 (2%)	1 (5%)	1 (2%)	3 (2%)
Died due to TB	0 (0%)	0 (0%)	1 (2%)	1 (1%)
Died due to other causes	0 (0%)	1 (5%)	1 (2%)	2 (2%)
Failed	0 (0%)	0 (0%)	1 (2%)	1 (1%)
Transferred out	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Unknown	2 (4%)	0 (0%)	0 (0%)	2 (2%)

PT: preventive treatment; MDR: multidrug resistant (isoniazid and rifampicin). [#]: row percentages are shown; [¶]: column percentages are shown; [+]: targeted active case finding in high-risk groups for TB, *i.e.* prison inmates, drug users or homeless persons; [§]: biannual screening in eligible persons with LTBI not receiving preventive treatment; [f]: International Statistical Classification of Diseases and Related Health Problems category Tuberculosis 010; [##]: percentages of culture-positive isolates are shown; [¶¶]: identical DNA fingerprint of mycobacterial isolate; [++]: unique DNA fingerprint of mycobacterial isolate; [§§]: diseases associated with a higher risk of progression to tuberculosis (HIV (n=1), malignancy (n=1), diabetes (n=5), immune suppressive medication (n=4), alcohol abuse (n=4), unspecified cause (n=1)).

with resistance to at least isoniazid was 14% (five out of 36) among culture-positive cases not receiving PT, 11% (three out of 27) among those completing PT and 8% (one out of 13) among those stopping PT. 93% of the patients with TB successfully completed TB treatment, one patient died from TB and two patients died from other causes.

Of 8871 persons completing PT, 57 (0.6%) developed TB, 28 of these cases developing TB before the end of PT. Of 5370 persons not receiving or completing PT, 77 (1.4%) developed TB: 21 (1.6%) out of 1167 persons who stopped PT and 56 (1.3%) out of 4203 persons not started on PT. Of 160 persons started on PT but stopped within 28 days, eight (5.0%) developed TB (odds ratio 8.2 (95% CI 3.8–15.5) compared with those completing PT). Of 5267 persons taking isoniazid monotherapy (6–9H) and rifamycin-containing regimens, 0.6% and 0.7% developed TB, respectively.

The average TB incidences among TB contacts were 187, 436 and 355 per 100 000 pyr for those completing PT, stopping PT and not receiving PT, respectively. For other target groups, the TB incidences were 69, 100 and 110 per 100 000 pyr, respectively. The incidence was highest during the first year after LTBI diagnosis. The TB incidence among TB contacts in the first year was 615, 1431 and 1155 per 100 000 pyr, respectively. For all other target groups, the risk for progression in the first year after diagnosis of LTBI was 175, 268 and 445 per 100 000 pyr among those who completed PT, who stopped PT and who did not receive PT, respectively (differences not significant) (figure 2).

The rate ratio of progression to TB, comparing TB contacts with other target groups, was 3.1 (95% CI 2.0–4.9) overall and 3.1 (95% CI 1.8–5.7) in the first year after LTBI diagnosis. The rate ratio comparing TB contacts completing PT and TB contacts stopping PT or not receiving PT in the first year was 0.43 (95% CI 0.22–0.89) and 0.53 (95% CI 0.32–0.90), respectively. In subsequent time periods following LTBI diagnosis, the incidence among TB contacts who did not receive (full) PT was also higher than among TB contacts who completed PT, but the difference was only statistically significant in the second year between those receiving PT and those not receiving PT, with a rate ratio of 0.13 (95% CI 0.03–0.45). Among other target groups, the rate ratio

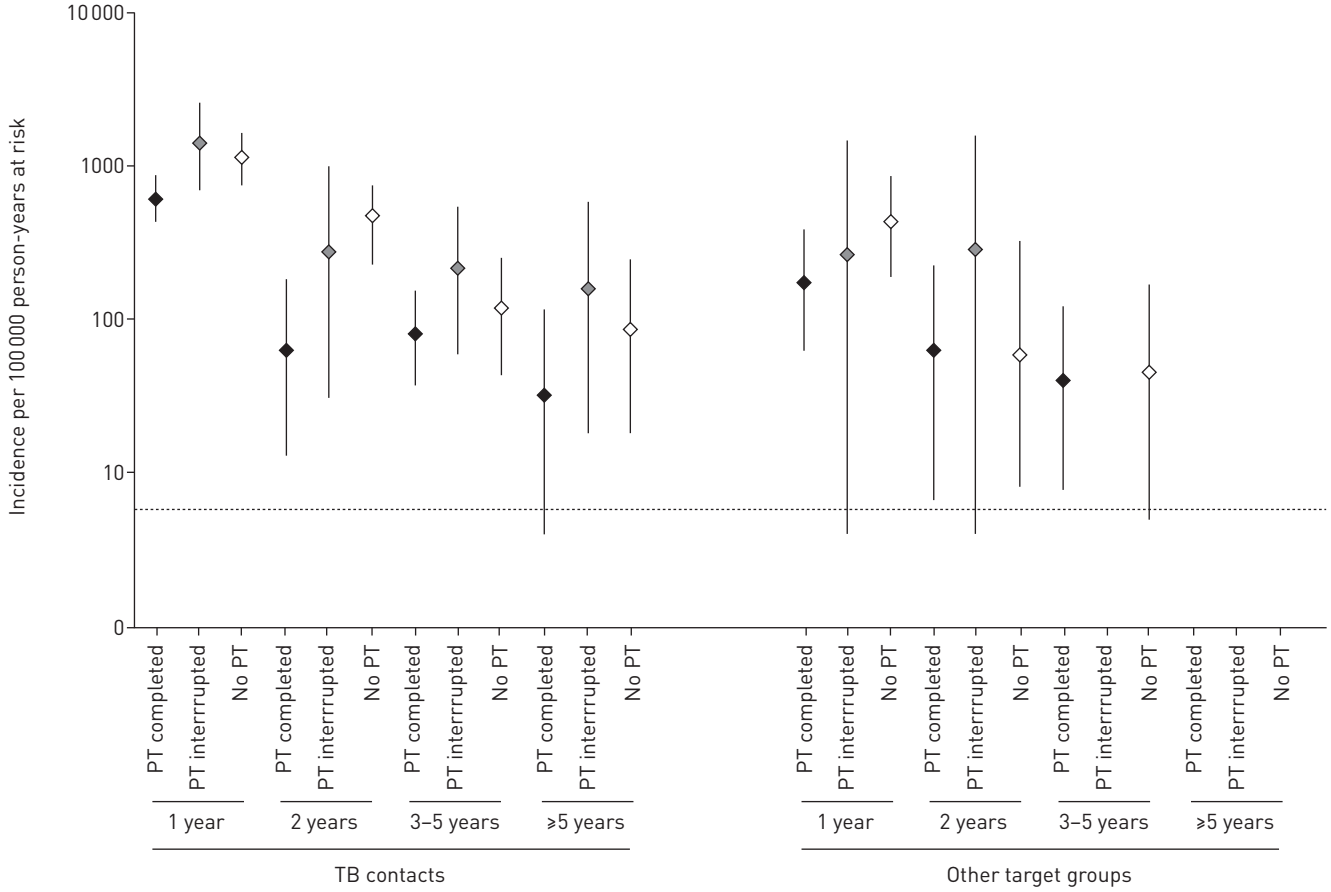

FIGURE 2 Incidence rates per 100 000 person-years at risk after latent tuberculosis infection (LTBI) diagnosis for tuberculosis (TB) contacts and other target groups by LTBI management group. PT: preventive treatment. Average TB incidence among the total Dutch population during study period was six per 100 000 population (dashed line).

DOI: 10.1183/13993003.01157-2016

comparing those completing PT and those stopping PT or not receiving PT was not significantly lower, even in the first year after diagnosis (p=0.14).

When 33 cases developing within 100 days after LTBI diagnosis were excluded, the incidence rate in the first year for TB contacts and other target groups completing PT was 192 and nine per 100 000 pyr, respectively. The overall rate ratio after this exclusion between those completing PT and those stopping PT or not receiving PT was 0.15 (95% CI 0.06–0.35) and 0.20 (95% CI 0.09–0.41), respectively, among TB contacts and 0.15 (95% CI 0.03–0.72) between other target groups completing PT and those not receiving PT. In the latter group, there were no TB cases observed among those who stopped PT.

Independent risk factors for developing TB among persons diagnosed with LTBI are presented in table 2. Patient characteristics associated with a higher risk of developing TB were age <5 years (adjusted hazard ratio (aHR) 2.9, 95% CI 1.3–6.2) and being a TB contact (aHR 3.3, 95% CI 1.9–5.7). Those who completed PT with isoniazid or a combined regimen of rifampicin and isoniazid had a lower risk (aHR

TABLE 2 Risk factors for developing tuberculosis (TB) after latent TB infection diagnosis, 2005–2013

	No active TB	Active TB	Univariable Cox regression		Multivariable Cox regression	
			HR (95% CI)	p-value	aHR (95% CI)	p-value
Total	14 107	134 (0.9%)				
Period						
2005–2007	5879	53 (0.9%)	1.0	0.05	1.0	0.07
2008–2010	4533	48 (1.1%)	1.4 (0.93–2.1)		1.5 (1.0–2.3)	
2011–2013	3695	33 (0.9%)	1.8 (1.1–2.8)		1.7 (1.0–2.9)	0.04[¶]
Sex						
Male	6909	72 (1.0%)	1.0	0.26		
Female	7183	62 (0.9%)	0.82 (0.59–1.2)			
Unknown[#]	15	0 (0.0%)				
Age group						
0–4 years	301	8 (2.6%)	3.2 (1.5–7.0)		2.9 (1.3–6.2)	
5–24 years	4341	36 (0.8%)	1.0	0.01	1.0	0.001
25–44 years	5366	57 (1.1%)	1.3 (0.87–2.0)		0.96 (0.63–1.5)	
⩾45 years	4099	33 (0.8%)	1.0 (0.64–1.6)		0.58 (0.35–0.96)	
Origin						
Dutch born	10 369	91 (0.9%)	1.0	0.03		
Foreign born	3738	43 (1.2%)	1.5 (1.1–2.2)			
BCG vaccination						
No BCG	9617	96 (1.0%)	1.0	0.95		
BCG	3069	27 (0.9%)	1.0 (0.67–1.6)			
BCG unknown	1421	11 (0.8%)	0.92 (0.49–1.7)			
Test						
TST	9268	96 (1.0%)	1.0	0.71		
IGRA	660	6 (0.9%)	1.2 (0.54–2.8)			
TST and IGRA	3983	29 (0.7%)	0.92 (0.60–1.4)			
Other method or unknown	196	3 (1.5%)	1.7 (0.54–5.43)			
Target group						
Contact investigation	8389	110 (1.3%)	2.9 (1.7–5.0)		3.3 (1.9–5.7)	
Immunosuppression	741	4 (0.5%)	1.3 (0.44–4.0)		2.0 (0.62–6.3)	
Pre-exposure	3295	15 (0.5%)	1.0	<0.001	1.0	<0.001
Post-exposure HCWs and travellers	1552	3 (0.2%)	0.41 (0.12–1.4)		0.44 (0.13–1.5)	
Fibrotic chest-radiographic abnormalities	130	2 (1.5%)	3.7 (0.85–16.3)		3.5 (0.78–15.9)	
Case management						
6–9H	5238	29 (0.6%)	0.38 (0.24–0.59)		0.32 (0.20–0.51)	
3–4RH, 4R, 2RZ or 2RHEZ	3393	25 (0.7%)	0.68 (0.42–1.1)		0.41 (0.24–0.68)	
Other	183	3 (1.6%)	1.3 (0.40–4.1)		0.97 (0.29–3.2)	
PT <28 days	152	8 (5.3%)	4.0 (1.9–8.3)		3.1 (1.5–6.6)	
PT ⩾28 days or more, or not completed	994	13 (1.3%)	0.93 (0.51–1.7)		0.73 (0.40–1.4)	
No PT	4147	56 (1.4%)	1.0	<0.001	1.0	<0.001

HR: hazard ratio; aHR: adjusted hazard ratio; BCG: bacille Calmette–Guérin; TST: tuberculin skin test; IGRA: interferon-γ release assay; HCW: healthcare worker; 6–9H: 6–9 months of isoniazid; 3–4RH: 3–4 months of rifampicin and isoniazid; 4R: 4 months of rifampicin; 2RZ: 2 months of rifampicin and pyrazinamide; 2RHEZ: 2 months of rifampicin, isoniazid, ethambutol and pyrazinamide; PT: preventive treatment. [#]: missing; [¶]: Wald test.

0.32 (95% CI 0.19–0.51 and 0.41 (95% CI 0.24–0.68), respectively) compared to those not receiving PT, while those stopping PT within 28 days had a higher independent risk (aHR 3.1, 95% CI 1.5–6.6). The difference between those completing the different PT regimens were not significant (p=0.42).

In the stratified analysis among TB contacts only, independent factors associated with the risk of developing TB were age <5 years (aHR 2.8, 95% CI 1.3–6.2) and case management method. TB contacts completing PT with isoniazid or a combined regimen with rifampicin and isoniazid had a reduced risk compared to those not receiving PT (aHR 0.27 (95% CI 0.16–0.45) and 0.53 (95% CI 0.31–0.89), respectively). Compared to those not receiving PT, contacts stopping PT within 28 days had the highest risk of developing TB (aHR 3.6, 95% CI 1.6–8.0). For other target groups, the only independent factor associated with the risk of developing TB was being foreign born (aHR 3.9, 95% CI 1.7–8.7).

In the sensitivity analysis of culture-positive TB only, TB contacts and those stopping PT within 28 days also had the highest independent risk of developing TB (aHR 3.6 (95% CI 1.7–7.5) and 4.3 (95% CI 1.8–10.2), respectively), while those completing PT with isoniazid- or a rifamycin-containing regimens had a reduced risk of developing culture-positive TB compared to those not receiving PT (aHR 0.35 (95% CI 0.20–0.62) and 0.27 (95% CI 0.12–0.61), respectively).

Discussion

Our study shows that the risk of developing TB varies widely in the populations targeted in the Netherlands for LTBI screening and PT. The incidence among contacts of infectious TB patients was three times higher than in other target groups. The strongest independent risk factors for developing TB in our population were age <5 years, being a TB contact and having received PT for <28 days. Among TB contacts, the risk of progression to TB was consistently lower among those completing PT than among those not receiving or not completing PT, in the overall, stratified and sensitivity analyses. PT reduced the incidence in the first year after diagnosis two-fold among TB contacts, but not significantly among other target groups identified with LTBI. For all target groups, the incidence remained higher than the background TB incidence of 5–6 per 100 000 in the Netherlands for ⩾5 years after LTBI diagnosis.

The rate observed among TB contacts was comparable to the rate reported among TB contacts in a TBNet study [7]. The risk of developing TB of 1.4% overall and 2.0% for TB contacts not receiving or completing PT observed in our study (table S2A) is lower than the estimated lifetime risks among infected individuals of 2–10% reported in the literature [5, 12–15]. There are several explanations for this. First, our study population is a mixed cohort of target groups for LTBI screening, with TB contacts and other target groups representing different exposure histories. Secondly, cases occurring within 28 days after LTBI diagnosis were not included in our study population, as the objective was to study the protective effect of PT and not the occurrence of TB after infection with *Mycobacterium tuberculosis*. Thirdly, in operational circumstances, there is selection and treatment bias, as those with the highest risk (TB contacts and young age groups) are more likely to receive PT. This was shown in another study using data from the same population [4] and is supported by the high risk of active TB in the group of persons in our study population stopping PT within 28 days. We observed a two-fold higher risk for TB contacts who did not complete or receive PT compared to those who completed PT. The protective effect of PT was markedly higher if cases with incident TB within 100 days after LTBI diagnosis were not included.

This is the first study using operational data comparing the effect of rifampicin-containing treatment regimens with isoniazid monotherapy. Consistent with a recent Cochrane review [16], we found that the shorter rifampicin-containing regimens are equivalent to isoniazid monotherapy in lowering the risk of progression to TB, with an aHR of 0.35 and 0.27, respectively. In the multivariate analysis, we combined 3–4 months of rifampicin and 3 months of rifampicin and isoniazid (3RH) in one category, with other rifampicin-containing regimens, but 74% of this category is actually 3RH. Since 2009, 3RH is the PT regimen increasingly preferred by both clinicians and patients in the Netherlands, with high rates of completion and low rates of adverse events causing interruption of PT compared to isoniazid monotherapy [4].

A limitation of the retrospective cohort design of our study is that LTBI cases have not been actively followed up. We assumed that all cases in the population were still alive and living in the Netherlands, thus overestimating the person-time of follow-up. This may have been different for different subgroups, thereby introducing bias. Such bias may, in particular, have been introduced for immunocompromised patients and the elderly (groups with an expected higher mortality), and foreign-born individuals and frequent travellers (who may have left the country). We also assumed all incident TB cases were notified to the NTR, thus possibly underestimating the number of incident TB cases. However, we believe the degree of such an underestimation is limited. In 1998, the adjusted undernotification of TB was estimated to be 7.3% in a capture–recapture study [17]. We expect the completeness of the NTR has improved since 2005, when a central web-based system was introduced and laboratory results were matched in real-time

 DOI: 10.1183/13993003.01157-2016

with the NTR. TB cases may also have been missed by the matching method as the possibility of matching of cases is limited when the LTBI case record number is not recorded in the anonymised TB register. On the other hand, for 15 cases, the likely match was not verified through a LTBI-registration number in the NTR. Cases may also have been overestimated through overdiagnosis as culture confirmation of the TB diagnosis among the cases was lower than the national average of 72% in this period [18], especially among cases who completed PT. In 57% of the cases, the diagnosis was based on the clinical picture, and in 28% of the cases, culture was not performed. This is common practice in the Netherlands: laboratory confirmation using invasive diagnostic procedures is often not pursued in asymptomatic persons with (recent) LTBI presenting with changes in the chest radiograph that are suspicious for TB, who fail to produce sputum. Through the sensitivity analysis exploring the risk factors for progression to culture positive TB only, we found that such bias does not affect the main conclusions of our study. The higher risk for children aged <5 years disappeared but this is to be expected since the rate of culture confirmation of the TB diagnosis in children <5 years is generally low [19].

The Netherlands has committed to the framework action plan towards TB elimination and to reach the goal of 25% reduction of TB incidence by 2020 [20]. In 2015, the TB incidence among the Dutch-born population was 1.3 per 100 000 [21]. However, in the last 25 years, the incidence has been influenced by the influx of immigrants from highly endemic areas, and 72% of the TB cases were foreign born. TB rates among newly arrived Somalians and Eritreans [22] are comparable to the rates observed in our study among untreated TB contacts. The national strategic plan for TB control in 2016–2020 aims to target immigrants from highly endemic areas for LTBI management, thus addressing the pool of persons infected with LTBI in the country.

Conclusion

Our study confirms that PT for LTBI reduces TB incidence in TB contacts, especially in the first 2 years after completing ⩾100 days of PT. In our low-incidence setting with a low number of high-priority target groups recommended by WHO, such as persons living with HIV, the effect of PT in other target groups was limited. Prompt examination and chemoprophylaxis or PT for TB contacts with a high risk of exposure and a high risk of progressing to TB, such as children <5 years of age and persons with immune compromising conditions, is crucial to effectively prevent TB cases. Extension of the intervention to lower priority target groups needs to be considered carefully.

Acknowledgements

The authors thank Nico Nagelkerke (Dept of Public Health, Erasmus Medical Center, Rotterdam, the Netherlands) for his advice on the approach of the statistical analysis. We also thank the staff of Municipal Public Health Centers for contributing the data and their support of persons treated for LTBI.

References

1 Uplekar M, Weil D, Lonnroth K, *et al.* WHO's new End TB Strategy. *Lancet* 2015; 385: 1799–1801.
2 Lönnroth K, Migliori GB, Abubakar I, *et al.* Towards tuberculosis elimination: an action framework for low-incidence countries. *Eur Respir J* 2015; 45: 928–952.
3 Getahun H, Matteelli A, Abubakar I, *et al.* Management of latent *Mycobacterium tuberculosis* infection: WHO guidelines for low tuberculosis burden countries. *Eur Respir J* 2015; 46: 1563–1576.
4 Erkens CG, Slump E, Verhagen M, *et al.* Monitoring latent tuberculosis infection diagnosis and management in the Netherlands. *Eur Respir J* 2016; 47: 1492–1501.
5 Morán-Mendoza O, Marion SA, Elwood K, *et al.* Risk factors for developing tuberculosis: a 12-year follow-up of contacts of tuberculosis cases. *Int J Tuberc Lung Dis* 2010; 14: 1112–1119.
6 Sloot R, Schim van der Loeff MF, Kouw PM, *et al.* Risk of tuberculosis after recent exposure. A 10-year follow-up study of contacts in Amsterdam. *Am J Respir Crit Care Med* 2014; 190: 1044–1052.
7 Zellweger JP, Sotgiu G, Block M, *et al.* Risk assessment of tuberculosis in contacts by IFN-gamma release assays. A Tuberculosis Network European Trials Group Study. *Am J Respir Crit Care Med* 2015; 191: 1176–1184.
8 Rangaka MX, Wilkinson RJ, Boulle A, *et al.* Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet* 2014; 384: 682–690.
9 Durovni B, Saraceni V, Moulton LH, *et al.* Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janeiro, Brazil: a stepped wedge, cluster-randomised trial. *Lancet Infect Dis* 2013; 13: 852–858.
10 A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. *Am Rev Respir Dis* 1992; 145: 36–41.
11 International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull World Health Organ* 1982; 60: 555–564.
12 Vynnycky E, Fine PE. Lifetime risks, incubation period, and serial interval of tuberculosis. *Am J Epidemiol* 2000; 152: 247–263.
13 Horsburgh CR Jr, O'Donnell M, Chamblee S, *et al.* Revisiting rates of reactivation tuberculosis: a population-based approach. *Am J Respir Crit Care Med* 2010; 182: 420–425.

14 Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol* 1974; 99: 131–138.
15 Sloot R, Schim van der Loeff MF, Kouw PM, *et al.* Risk of tuberculosis after recent exposure. A 10-year follow-up study of contacts in Amsterdam. *Am J Respir Crit Care Med* 2014; 90: 1044–1052.
16 Sharma S, Sharma A, Kadhiravan T, *et al.* Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. *Cochrane Database Syst Rev* 2013; 7: CD007545.
17 van Hest NA, Smit F, Baars HW, *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.
18 KNCV Tuberculosis Foundation. TBC-online. www.tbc-online.nl/eng/ziekte/index.php Date last updated: July 2015.
19 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.
20 De Vries G, Riesmeijer R. Nationaal Plan Tuberculosebestrijding 2016-2020. Op weg naar eliminatie. [National Plan TB control 2016-2020. Towards Elimination.] Bilthoven, Rijksinstituut voor Volksgezondheid en Milieu, 2016.
21 Slump E, Erkens CGM, Van Hunen R, *et al.* Tuberculose in Nederland 2014. Surveillance rapport. [Tuberculosis in the Netherlands 2014. Surveillance report.] Bilthoven, Rijksinstituut voor Volksgezondheid en Milieu, 2015.
22 de Vries G, Gerritsen RF, van Burg JL, *et al.* Tuberculose bij asielzoekers in Nederland [Tuberculosis among asylum-seekers in the Netherlands: a descriptive study among the two largest groups of asylum-seekers]. *Ned Tijdschr Geneeskd* 2016; 160: D51.

DOI: 10.1183/13993003.01157-2016