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1. Title

Risk of tuberculosis after recent exposure: a 10-year follow-up study of contacts in Amsterdam

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5. Authors' contributions

Conception and design- RS, MFS, PMK, MWB; Data acquisition- RS, MFS, PMK, MWB; Data analysis and interpretation- RS, MFS, PMK, MWB; Manuscript preparation- RS, MFS, PMK, MWB.

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Risk of tuberculosis: a 10-year follow-up study

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10. At a Glance Commentary

Scientific knowledge on the subject

It is often stated that in the absence of preventive therapy 10% of individuals who acquire latent tuberculosis infection (LTBI) will develop tuberculosis (TB), of which 5% within 5 years of infection. Similar estimates of TB activation are often used in cost-effectiveness studies assessing the benefits of preventive TB therapy, but these estimates are based on the risk of TB observed decades ago and may not be applicable in all settings.

What this study adds to the field

The risk of TB was assessed in a low-incidence, high-income setting among contacts of pulmonary TB patients using 10 years of follow-up data. The 5-year risk of incident TB among contacts with LTBI and without preventive therapy was low at 2.4%, suggesting the need to reassess cost-effectiveness estimates of preventive TB therapy.

11. There is no online data supplement

Abstract

Rationale:

The lifetime risk of tuberculosis (TB) for infected contacts is often mentioned to be 5 to 10 percent, but these estimates are based on studies conducted decades ago, thus may not reflect current epidemiological conditions.

Objective:

To estimate the risk of TB among contacts with evidence of infection and to compare this with estimates often stated in the literature.

Methods:

A retrospective cohort study was performed using records on contacts of pulmonary TB (PTB) patients at the Public Health Service Amsterdam (PHS), 2002-2011. The PHS-TB electronic registration system identified TB cases during follow-up until October 2012; these were defined as co-prevalent if diagnosed ≤180 days and incident if diagnosed >180 days after TB diagnosis of index patient. Cumulative TB risk was estimated with Kaplan-Meier curves.

Result:

Of 9,332 contacts of PTB patients, 4,774 were screened for LTBI of whom 739 (16%) had evidence of infection. Among these the 5-year Kaplan-Meier TB cumulative risk was 9.5% (95%CI=7.5-11.9); this varied by age: 33.3% of 36 contacts aged <5 years, 19.1% of 84 contacts aged 5-14 years, and 6.7% of 619 contacts aged ≥15 years (log rank, P<0.001). Of

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739 contacts with evidence of infection, 57 had co-prevalent TB and 14 developed incident TB. Of patients without co-prevalent TB but with LTBI diagnosis, 45% received preventive therapy. Five-year risk of incident TB was 2.4% (95%CI=1.2-4.7) among contacts with LTBI who did not start preventive therapy.

Conclusions:

Five-year risk of TB among contacts with evidence of infection was higher compared to older estimates, and differed considerably by age. Incidence of TB among contacts with LTBI was low, suggesting limited impact may be expected of expanding preventive therapy.

Number of words abstract: 270

Key words: tuberculosis contact investigation, tuberculosis incidence, preventive therapy, follow-up

Introduction

Eligibility for preventive therapy among individuals recently exposed to a known tuberculosis (TB) patient depends on the degree of exposure, infectiousness of the source case, age of the exposed individual, estimated risk of progression to disease, and (cost-) effectiveness and risk of adverse effects of preventive therapy (1). It is often stated that the risk of TB for persons with a positive tuberculin skin test (TST) is 10 percent, of which 5% within 5 years of infection (2). Cost-effectiveness analyses assessing the benefits of preventive therapy, generally use similar estimates of TB risk (3) (4) (5) (6). However, these estimates are based on TB rates observed decades ago (7) (8) (9) (10) (11), thus may not reflect current epidemiological conditions, and may not be applicable in all settings, and could be modified by preventive therapy, BCG vaccination, or age (12) (13) (14). For instance, the risk of reactivation TB in Hong Kong was much higher than in the UK (15), and the risk of developing TB after exposure is often higher in low-income countries as compared to high-income countries (16).

This study had four objectives. First, to determine risk factors for co-prevalent TB and incident TB among contacts exposed to pulmonary tuberculosis (PTB) patients in Amsterdam, a low TB incidence, high-income setting. Second, to estimate the risk of TB among contacts with evidence of infection. Third, to obtain a TB incidence estimate among

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contacts with latent tuberculosis infection (LTBI) and, finally, to compare observed TB risk estimates to estimates generally used in cost-effectiveness analyses.

Methods

Study design

We conducted a retrospective cohort study using ten years of public health surveillance data from the tuberculosis control department of the Public Health Service (PHS) in Amsterdam. Follow-up results of individuals traced and examined in the course of a contact investigation of PTB index patients were included. The electronic TB patient and client registration system at the PHS Amsterdam was used to ascertain whether a contact developed TB during follow-up.

Contact investigations

In the city of Amsterdam, the diagnosing physician notifies the PHS of a patient diagnosed with TB. Demographic information including gender and date of birth is recorded. In addition, clinical and laboratory information is collected, including details on HIV infection, type of TB (pulmonary or extrapulmonary), results of sputum smears, sputum culture, and *M. tuberculosis* genotype results. Since 2004, variable number tandem repeat (VNTR) typing is performed on *M. tuberculosis* isolates recovered from all TB patients in the Netherlands

according to the international standard (17). Before 2004, restriction fragment length polymorphism (RFLP) typing was performed (18).

In order to evaluate the risk of transmission, a nurse at the tuberculosis control department of the PHS interviews the patient and enquires about persons with whom the patient has had recent contact. The PHS then starts a source and contact investigation. The PHS staff investigates recent contacts of PTB index patients and evaluates duration and frequency of exposure to the index patient during the infectious period. Accordingly, contacts are listed as first ring, second ring, third ring, and so forth (contacts in rings beyond the second ring are categorised as casual contacts) based on national guidelines for contact investigation (19). Screening for latent tuberculosis infection (LTBI) and for TB starts among first ring contacts of PTB patients. Depending on the infection and disease prevalence among first ring contacts of smear-positive PTB index patients, second ring and eventually possibly casual contacts are also invited for screening.

LTBI screening includes a tuberculin skin test (TST) and chest radiograph. The TST is done by intradermal injection of 2 Units PPD-RT23 on the volar side of the forearm. After 72 to 96 hours the size of the diameter of the induration at the site of injection is measured in millimetres. Since the introduction of the interferon gamma release assay (IGRA) in 2008, national guidelines indicate that the IGRA should be used to validate a positive TST result

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(20). At the PHS Amsterdam the QuantiFERON-TB (QFT) (QFT-GIT; Cellesis, Carnegie, Australia) is used, which measures the production of interferon gamma (IFN-g) after T cells are exposed *in vitro* to a *M. tuberculosis*-specific antigen mix; a QFT is considered positive if ≥0.35 IU/ml (21).

If a TB diagnosis is made, the TB control physician prescribes anti-tuberculosis therapy. Contacts with an LTBI diagnosis are offered preventive therapy (either 3 months isoniazid and rifampicin, or 6 months isoniazid, or 4 months rifampicin), or, if contra-indicated, follow-up of contacts at risk of progression to TB is proposed for a duration of two years.

Contacts

The electronic TB patient and client registration system at the PHS Amsterdam was used to identify all individuals that were traced and examined in the course of contact investigations of PTB index patients diagnosed from January 2002 through June 2011. Contacts were included if they were traced and examined ≤180 days after the TB diagnosis of the index patient. This period was chosen because it takes up to 180 days to identify, evaluate, diagnose and initiate preventive therapy for contacts by the PHS Amsterdam. Contacts were excluded if their residence at the time of the examination was outside the Amsterdam region.

Data collected during contact investigations included gender, date of birth, nationality, relationship between contacts and index patients (first ring, second ring, or casual contact), BCG vaccination status, TST and IGRA results, and data on initiation of preventive TB therapy.

Study outcomes

The notification date of the PTB index patient was used as the start of follow-up of the contact. Whether a contact developed TB during follow-up was ascertained using data in the electronic registration system at the PHS Amsterdam until October 6, 2012. Follow-up was censored if the contact was notified as TB patient (event), or if an individual was identified as a contact in a subsequent contact investigation.

Definitions

Contacts were considered eligible for LTBI screening in accordance with national guidelines: being a contact of a sputum smear-positive PTB patient or being a first ring contact of a smear-negative PTB patient; all contacts had to be born after 1945 (19). Contacts were considered screened for LTBI if a TST or an IGRA was done. Contacts were regarded as having LTBI if IGRA was positive. In the absence of IGRA results, contacts with TST ≥10 mm were considered as having LTBI. A TB diagnosis was made by clinicians, based on symptoms, chest X-ray, sputum smear and culture results, and/or by clinical response to

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treatment, based on national guidelines (19). Contacts diagnosed with TB ≤180 days after an index patient's TB diagnosis were considered 'co-prevalent' cases. TB diagnosed in contacts >180 days after an index patient's TB diagnosis were considered 'incident' cases. We compared *M. tuberculosis* genotype results of TB index patients and their contacts diagnosed with TB.

Statistical analysis

A probabilistic record linkage procedure was performed to determine which contacts developed TB during the study period. One dataset contained records of all TB patients notified to the PHS Amsterdam from January 2002 through October 2012, and a second dataset contained records of all contacts that were traced and examined in the course of contact investigations of PTB index patients from January 2002 till June 2011. Linking variables were used to determine the probability of a match and included registration number, name and surname, postal code, date of birth, sex, and nationality. The posterior probability was calculated similar to Schaaf et al., and denoted the probability of agreement for each variable among the matches and non-matches (22). A probability higher than 80% was considered high enough to assume that the contact and TB patient were the same person, provided they were not part of the same family (22) (23). Record linkage resulted in 110 matches with a 100% probability and 14 matches with a posterior probability between 80%

and 100%. Verification of these matches revealed in all 14 instances that they were different individuals.

Demographic, laboratory, and clinical determinants (both index-patient and contact-related) for co-prevalent tuberculosis were identified using logistic regression. In order to account for correlated data (multiple contacts belonging to the same index patient in a contact investigation) *generalized estimating equations* (GEE) were used. Kaplan-Meier curves were used to estimate cumulative TB risk. Clustered Cox proportional hazards regression (24) was used to calculate crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of incident TB. TB incidence was also reported as 5-year cumulative TB risk, excluding cases diagnosed in the first 180 days; co-prevalent TB cases were excluded from this analysis, as were contacts identified in a subsequent contact investigation within 180 days. Variables that were associated with the outcome in univariable analysis at $P<0.2$ were included in a multivariable model. Variables were subsequently eliminated from the model if they did not have an independent association with the outcome and their exclusion did not substantially affect the estimates of the other variables. Sex and age, of both index and contact, were a priori kept in the models and the level of significance in all analyses was $P<0.05$. Analyses were completed in SPSS 21.0 (SPSS, Chicago, IL, USA), Stata (version 13.0; Stata Corp, College Station, TX, USA), and statistical programme R version 2.11.0 (R Foundation, Vienna, Austria).

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Results

Study population

In the period 2002-2011, there were 9,332 contacts of 610 index patients with PTB. Of these 9,332 contacts, 5,867 (63%) had a male index patient, 355 (4%) had an index patient aged below 15 years, 7,120 (76%) had a smear-positive TB index patient, and 634 (7%) had an HIV-positive index patient (Table 1). Of the 9,332 contacts, 4,492 (48%) were male, 1,519 (16%) were aged below 15 years, 6,398 (69%) were of Dutch nationality, 6,234 (67%) were first or second ring contacts, and 3,011 (32%) had evidence of BCG vaccination (Table 1).

Co-prevalent TB among contacts

In the study period, 74 of 9,332 contacts (0.8%) had co-prevalent TB (Table 1). Co-prevalent TB was not associated with sex of the index patient, but was less likely if the index patient was aged 0-14 years (aOR=0.1, 95%CI=0.02-0.8) or aged ≥45 years (aOR=0.4, 95%CI=0.2-0.8) as compared to age 15-44 years (Table 1). Co-prevalent TB was less likely among contacts of smear-negative index patients (aOR=0.3, 95%CI=0.1-0.7).

Co-prevalent TB was not associated with sex of contact, but was lower in adults as compared to contacts aged ≤14 years (aOR age 15-44 years=0.3, 95%CI=0.1-0.5, aOR age ≥45

years=0.2, 95%CI=0.1-0.5) (Table 1). The odds of co-prevalent TB declined with decreasing intensity and duration of contact: compared with first ring contacts, the aOR was 0.2 (95%CI=0.1-0.4) for second ring contacts and 0.07 (95%CI 0.01-0.6) for casual contacts (Table 1).

Incident TB among contacts

Contacts with co-prevalent TB diagnosed during the contact investigation (n=74) and contacts identified in a subsequent contact investigation ≤180 days after index TB diagnosis (n=45) were excluded from the analysis of incident TB. Among the remaining 9,213 contacts, 36 (0.4%) TB cases were identified in the study period.

Incident TB was not associated with sex of the index patient, but was less likely if the index patient was aged ≥45 years as compared to age 15-44 years (aHR=0.1, 95%CI=0.05-0.6) (Table 2). TB incidence was not associated with sex and age of the contact. Incident TB was less likely if contacts were second ring contacts or casual contacts as compared to first ring contacts (aHR=0.2, 95%CI=0.08-0.7). BCG-vaccinated contacts were more likely to have incident TB compared to contacts without evidence for BCG vaccination (aHR=2.3, 95%CI=1.1-5.1) (Table 2).

Contacts without LTBI were significantly less likely to be diagnosed with incident TB than contacts with LTBI diagnosis who did not start preventive therapy (aHR=0.08, 95%CI=0.02-

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0.3) (Table 2). There was no significant reduction in incident TB among contacts with LTBI who started preventive therapy (aHR=0.8, 95%CI=0.2-2.7).

Cumulative TB risk among contacts with evidence of infection

During the contact investigation 739 (16%) of the 4,774 contacts screened for LTBI had evidence of infection (Figure 1a). Among these 739 contacts, 57 had co-prevalent TB and 14 developed incident TB. The 5-year risk of co-prevalent and incident TB among 739 contacts with evidence of infection was 9.5% (95%CI=7.5-11.9) (Figure 2). Among 739 contacts, 36 contacts were aged <5 years, of whom 11 had co-prevalent TB and 1 had incident TB; 84 were aged 5-14 years, of whom 14 had co-prevalent TB and 2 had incident TB, and of the 619 contacts aged ≥15 years, 32 had co-prevalent TB and 11 had incident TB (Figure 3). The 5-year risk of co-prevalent and incident TB was 33.3% (95%CI=19.1-51.1) among contacts aged <5 years, 19.1% (95%CI=11.6-29.4) among contacts aged 5-14 years, and 6.7% (95%CI=4.9-9.1) among contacts aged ≥15 years (log rank, P<0.001) (Figure 3).

Cumulative TB risk among contacts with LTBI

Among 739 contacts with evidence of infection, 681 had LTBI and were eligible for preventive therapy, of whom 309 (45%) started preventive therapy (Figure 1a). For the contacts with LTBI, the 5-year risk of incident TB was 2.4% (95%CI=1.2-4.7) among contacts who did not start preventive therapy and 1.4% (95%CI=0.03-3.6) among contacts

who started preventive therapy (Table 2). Among 381 first ring contacts with evidence of infection, 347 contacts had LTBI and were eligible for preventive therapy, of whom 146 (42%) started preventive therapy (Figure 1b). For the first ring contacts with LTBI, the 5-year risk of incident TB was 3.5% (95%CI=1.5-7.3) among contacts who did not start preventive therapy and 0.7% (95%CI=0.05-4.4) among contacts who started preventive therapy.

Genotypes of index and contact

Culture status was available for 81 of 110 contacts diagnosed with TB, of whom 43 (53%) were culture-positive (Table 3). Of the 17 TB cases among contacts aged below 5 years, culture status was not available for 12, and the remaining 5 cases were culture-negative. The proportion of contacts with culture-confirmed tuberculosis among contacts aged ≥5 years was smaller for cases diagnosed within 6 months (47%) compared with those diagnosed later. For 35 (81%) of 43 contacts aged ≥5 years with TB diagnosis confirmed by culture a *M. tuberculosis* genotype was available for both index and contact, of whom 29 (83%) had concordant genotypes (Table 3). Genotype concordance among cases diagnosed within 2 years was higher as compared to concordance among cases diagnosed >2 years (93% versus 50%).

Discussion

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The 5-year risk of TB among contacts with evidence of infection was higher compared to older estimates, and the risk of TB differed considerably by age. Furthermore, the 5-year risk of incident TB among contacts with LTBI and without preventive therapy was low at 2.4%, suggesting limited impact of expanding preventive therapy. These results suggest that the risk of TB might vary considerably between populations.

TB risk estimates in cost-effectiveness studies often rely on TB rates based on data collected decades ago, estimated at 5 to 10 percent (7) (8) (9) (10) (11). These estimates include both 'co-prevalent' and 'incident' TB; thus cost-effectiveness studies do not take into account that contacts with co-prevalent TB, diagnosed during contact investigation, are unlikely to benefit from preventive TB therapy, indicating that typical cost-effectiveness studies might be overestimating the benefits of preventive therapy and its cost-effectiveness. In this study, the 5-year risk of incident TB without preventive treatment was limited at 2.4% after exclusion of co-prevalent TB cases, suggesting limited potential impact of preventive therapy. Although the 5-year risk of incident TB was higher among first ring contacts of index patients, the risk (3.5%) was still lower than estimates generally used in cost-effectiveness analyses.

TB incidence in placebo groups from controlled trials among TST reactors of household contacts of infectious TB cases in United States, Kenya and Philippines were summarized in

a review by Ferebee and differed considerably from each other (respectively: 2.2% after 5 years, 4.8% after 4 years and 14% after 2 years) and from TB incidence in our analysis among close contacts who did not start preventive therapy (3.9% after 10 year) (7). Despite differences in follow-up, size of population and diagnostic criteria, variation in rates may reflect real differences in TB risk between populations. The risk of TB may also vary across settings depending on the age distribution. The 5-year TB risk among contacts with evidence of infection in our study was higher than the 5% often stated in literature. However, 84% of our study population was aged ≥15 years, and the 5-year TB risk of 6.7% in this age group was close to estimates often mentioned in literature (2) (7) (9). Children are, once infected, at a much higher risk of progression to TB than adults (25). In our study, the risk of co-prevalent and incident TB among contacts with LTBI aged <5 years was about twice the risk among contacts aged 5-14 years, and the risk among contacts aged 5-14 years was almost three times the risk among contacts aged ≥15 years.

TB diagnosis in children is generally very difficult, which was also apparent in our study as the majority of TB diagnoses among contacts aged <5 years were not confirmed by culture. Thus no genotype results were available to investigate concordance with index genotypes.

More than half of the contacts diagnosed with LTBI did not start preventive therapy. Although the 5-year risk of TB was lower among those who were prescribed preventive

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therapy, the risk was not significantly lower compared to those who were not prescribed prophylaxis. This could be due to limited power, but also by confounding by indication as treatment allocation was not randomized and may well have been associated with the risk of TB. Also, we might have underestimated the impact of therapy, as we did not take into account treatment completion. Incomplete therapy could, as shown by a study from Canada, result in a 6-fold higher risk of TB among contacts as compared to contacts who complete therapy (26).

Current Dutch guidelines restrict LTBI screening among smear-negative patients to first ring contacts. Contacts of sputum smear-negative index patients were significantly less likely to be diagnosed with co-prevalent TB. Likewise, the prevalence of co-prevalent TB was extremely low among casual contacts of smear-positive index patients, and none of the casual contacts developed incident TB. A cost-effectiveness analysis may indicate whether screening among first ring contacts of smear-negative index patients and casual contacts of smear-positive index patients is worthwhile.

This study has some limitations. First, by using a uniform TST cut-off of ≥10 mm for LTBI diagnosis we may have under- or overestimated the number of contacts with LTBI at risk for TB, which could have influenced the observed impact of preventive treatment. However, TST reactions caused by previous BCG vaccination or infection with nontuberculous

mycobacteria (NTM) are expected to be of limited influence (27) (28). Second, as country of birth was unknown to us, it was impossible to correct for background infection prevalence among contacts from high TB burden countries which might be useful as LTBI diagnosis among these contacts might be due to remote past infection. However, it has been demonstrated that among immigrant contacts of TB patients, the TST is indicative in predicting the risk of developing TB, irrespective whether a cut-off value for the TST of 10 mm or 15 mm was used, justifying preventive treatment in this group (29). Third, we did not take into account that a small proportion of the contacts will have passed away during the follow-up period. This will have resulted in a small overestimation of the people at risk, leading to an underestimation of the cumulative TB risk. Fourth, we did not take into account that a proportion of the people at risk will have moved out of Amsterdam during the study period. Assuming that moving is not associated with risk of TB, this would have led to proportional decreases of people at risk and TB cases identified, but not to biased risk estimates. Finally, a 180 day cut off was used to allow time for diagnosis of active TB cases among contacts or initiation of chemoprophylaxis for infected contacts, and may have resulted in an underestimation of incident TB cases among contacts with LTBI. However, our aim was to estimate the risk of TB among contacts eligible for preventive therapy, and contacts in whom TB was diagnosed within 180 days of the TB diagnosis in the index were most likely non-preventable cases.

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This study has some important strengths. This is one of the few cohort studies in recent decades examining long-term outcomes of contact investigation for which robust data analysis of a large number of contacts was possible due to the PHS' systematized TB control programme. Furthermore, genotyping results provided assurance that the majority of TB among contacts likely resulted from exposure to their index patient.

In conclusion, this study showed that in a low-TB incidence and low-HIV prevalence, high-income setting, the risk of progression to TB among contacts with LTBI is low, suggesting limited impact may be expected of expanding preventive therapy. Therefore, future studies assessing the cost-effectiveness of preventive therapy among contacts with LTBI should acknowledge the potential influence of setting-dependent factors.

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Figure legends

Legend Figure 1:

Eligible for LTBI screening: contacts of sputum smear-positive PTB patients or first ring contacts of smear-negative PTB patients; only contacts born after 1945.

LTBI screening: if a tuberculin skin test (TST) or an interferon gamma release assay (IGRA) was done.

LTBI diagnosis: IGRA-positive, or in the absence of an IGRA result, TST ≥10 mm.

Co-prevalent TB: tuberculosis (TB) in contact if diagnosed ≤180 days of TB diagnosis of index patient.

Incident TB: TB in contact if diagnosed >180 days of TB diagnosis of index patient.

Figure 1a. Flow chart of contacts of pulmonary tuberculosis index patients, Amsterdam 2002-2011.

Figure 1b. Flow chart of first ring contacts of pulmonary tuberculosis index patients, Amsterdam 2002-2011.

Figure 2. TB risk among 739 contacts with evidence of infection at risk for co-prevalent and incident TB after exposure to pulmonary tuberculosis index patients.

Figure 3. TB risk among 739 contacts with evidence of infection at risk for co-prevalent and incident TB after exposure to pulmonary tuberculosis index patients, by age.

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Table 1. Risk factors for co-prevalent tuberculosis among 9,332 contacts of pulmonary tuberculosis patients.

		Contacts with co-prevalent TB n (%)	Contacts without co-prevalent TB n (%)	Crude Odds Ratio (95%CI)	Adjusted Odds Ratio (95%CI)
		74 (0.8)	9,258 (99.2)		
Index factors					
Sex					
	Male	42 (0.7)	5,825 (99.3)	1	1
	Female	32 (0.9)	3,433 (99.1)	1.1 (0.6-2.1)	1.0 (0.6-1.8)
Age, years [a]					
	0-14	1 (0.3)	354 (99.7)	0.1 (0.03-0.9)	0.1 (0.02-0.8)
	15-44	60 (1.1)	5,304 (98.9)	1	1
	45-64	11 (0.4)	2,695 (99.6)	0.3 (0.1-0.5)	0.4 (0.2-0.8)
	≥65	2 (0.2)	905 (99.8)		
Sputum smear status					
	Smear-positive	68 (1.0)	7,052 (99.0)	1	1
	Smear-negative	5 (0.3)	1,491 (99.7)	0.3 (0.1-0.8)	0.3 (0.1-0.7)
	Unknown	1 (0.1)	715 (99.9)	0.1 (0.02-1.1)	0.1 (0.02-1.1)
HIV status					
	Negative	12 (0.9)	1,328 (99.1)	1	
	Positive	1 (0.2)	633 (99.8)	0.2 (0.02-1.8)	
	Unknown	61 (0.8)	7,297 (99.2)	0.8 (0.3-2.1)	
Contact factors					
Sex [b]					
	Male	37 (0.8)	4,455 (99.2)	1	1
	Female	37 (0.8)	4,672 (99.2)	0.8 (0.5-1.4)	1.0 (0.6-1.5)

Age, years [a, b]				
0-14	30 (2.0)	1,489 (98.0)	1	1
15-44	33 (0.7)	4,994 (99.3)	0.3 (0.1-0.6)	0.3 (0.1-0.5)
45-64	9 (0.4)	2,406 (99.6)	0.2 (0.09-0.4)	0.2 (0.1-0.5)
≥65	2 (0.6)	357 (99.4)		
Nationality				
Dutch	58 (0.9)	6,340 (99.1)	1	
Other	16 (1.0)	1,619 (99.0)	1.0 (0.4-2.7)	
Unknown	0	1,299 (100.0)		
Type of contact				
First ring	37 (1.5)	2,405 (98.5)	1	1
Second ring	16 (0.4)	3,776 (99.6)	0.2 (0.1-0.5)	0.2 (0.1-0.4)
Casual contact	1 (0.1)	845 (99.9)	0.05 (0.002-1.6)	0.07 (0.01-0.6)
Unknown	20 (0.9)	2,232 (99.1)	0.5 (0.2-1.1)	0.4 (0.2-0.9)
BCG				
No evidence of BCG vaccination/ unknown	49 (0.8)	6,272 (99.2)	1	
Evidence of BCG vaccination	25 (0.8)	2,986 (99.2)	1.0 (0.5-2.0)	

[a] Index and contact age groups 45-64 and ≥65 are combined in the univariable and multivariable analysis.
[b] Category unkown sex contact (n=132) and category unkown age contact (n=12) are not shown.

Footnote
Co-prevalent TB: TB in contact if diagnosed ≤180 days of TB diagnosis of index patient.
BCG: Bacille Calmette–Guérin

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Table 2. Risk factors for incident tuberculosis among 9,213 contacts of pulmonary tuberculosis patients.

		Incident TB cases (n)	5-year TB risk	Crude Hazard Ratio (95%CI)	Adjusted Hazard Ratio (95%CI)
		36	0.3 (0.2-0.5)		
Index factors					
Sex					
	Male	24	0.4 (0.3-0.6)	1	1
	Female	12	0.3 (0.1-0.5)	0.8 (0.4-1.7)	0.8 (0.4-1.6)
Age, years [a]					
	0-14	2	0.3 (0.02-1.8)	0.8 (0.2-3.1)	1.3 (0.3-5.9)
	15-44	31	0.5 (0.4-0.8)	1	1
	45-64	2	0.07 (0.01-0.3)	0.1 (0.04-0.4)	0.1 (0.05-0.6)
	≥65	1	0.1 (0.01-0.7)		
Sputum smear status					
	Smear-positive	31	0.4 (0.3-0.6)	1	
	Smear-negative	3	0.2 (0.05-0.6)	0.4 (0.1-1.5)	
	Unknown	2	0.2 (0.01-0.9)	0.6 (0.1-2.4)	
HIV status					
	Negative	7	0.8 (0.4-1.5)	1	
	Positive	3	0.5 (0.1-1.5)	0.5 (0.1-2.4)	
	Unknown	26	0.3 (0.2-0.4)	0.4 (0.1-1.1)	
Contact factors					
Sex [b]					
	Male	19	0.4 (0.2-0.6)	1	1
	Female	17	0.3 (0.2-0.6)	0.8 (0.4-1.5)	0.9 (0.4-1.7)
Age, years [a, b]					
	0-14	5	0.4 (0.1-0.9)	1	1

	15-44	26	0.5 (0.3-0.7)	1.6 (0.6-3.9)	1.6 (0.6-4.7)
	45-64	4	0.1 (0.02-0.3)	0.5 (0.1-1.8)	0.9 (0.2-3.5)
	≥65	1	0.3 (0.02-1.8)		
Nationality					
	Dutch	23	0.3 (0.2-0.5)	1	
	Other	11	0.7 (0.3-1.2)	1.7 (0.8-3.6)	
	Unknown	2	0.2 (0.03-0.6)	0.4 (0.08-1.9)	
Type of contact [c]					
	First ring	16	0.7 (0.4-1.1)	1	1
	Second ring	5	0.1 (0.05-0.3)	0.1 (0.06-0.4)	0.2 (0.08-0.7)
	Casual contact	0	0		
	Unknown	15	0.5 (0.2-0.9)	0.7 (0.3-1.4)	0.7 (0.3-1.7)
BCG					
	No evidence of BCG vaccination/ unknown	12	0.2 (0.1-0.3)	1	1
	Evidence of BCG vaccination	24	0.7 (0.2-1.0)	4.2 (2.1-8.4)	2.3 (1.1-5.1)
Preventive therapy by LTBI status					
	Eligible for screening; LTBI & no therapy	10	2.4 (1.2-4.7)	1	1
	Eligible for screening; LTBI & therapy started	4	1.4 (0.03-3.6)	0.5 (0.1-1.7)	0.8 (0.2-2.7)
	Eligible for screening; no LTBI	4	0.1 (0.03-0.3)	0.03 (0.01-0.1)	0.08 (0.02-0.3)
	Other [d]	18	0.3 (0.2-0.5)	0.1 (0.06-0.3)	0.2 (0.1-0.6)

[a] Index and contact age groups 45-64 and ≥65 were combined in the univariable and multivariable analysis.
[b] Category unkown sex contact (n=130) and category unkown age contact (n=12) are not shown.
[c] Second ring and casual contacts were combined in the univariable and multivariable analysis.
[d] Contacts eligible for LTBI screening but not screened, or contacts not eligible for LTBI screening, or if LTBI screening eligibility was unknown.

Footnote
BCG: Bacille Calmette–Guérin
LTBI: Latent tuberculosis infection

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Table 3. ***M. tuberculosis*** **genotyping results of co-prevalent and incident tuberculosis among contacts of pulmonary tuberculosis patients by time since exposure and age of contact.**

	Time since index TB diagnosis (years)	Total TB cases *n*	Culture status available *n*	Culture-positive *n (%)*	Culture-positive and genotype results available for index and contact *n*	Concordant genotypes *n (%)*
Age contact						
<5 years	0-0.5	16	5	0		
	>0.5-2	1	0			
	>2	0				
≥5 years	0-0.5	58	43	20 (47)	16	15 (94)
	>0.5-2	21	19	12 (63)	11	10 (91)
	>2	14	14	11 (79)	8	4 (50)
Total		**110**	**81**	**43 (53)**	**35**	**29 (83)**

Figure 1a.

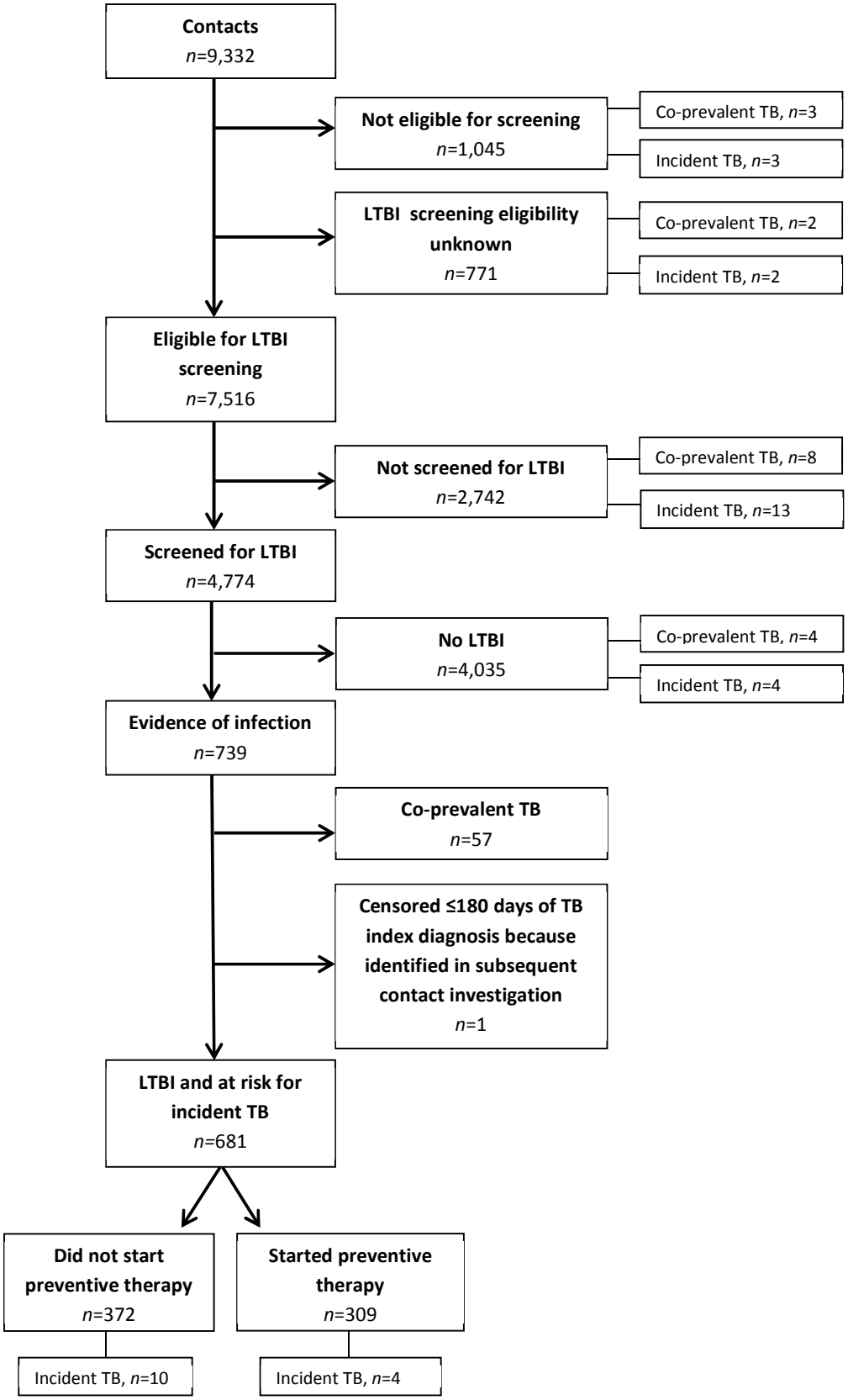

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Figure 1b.

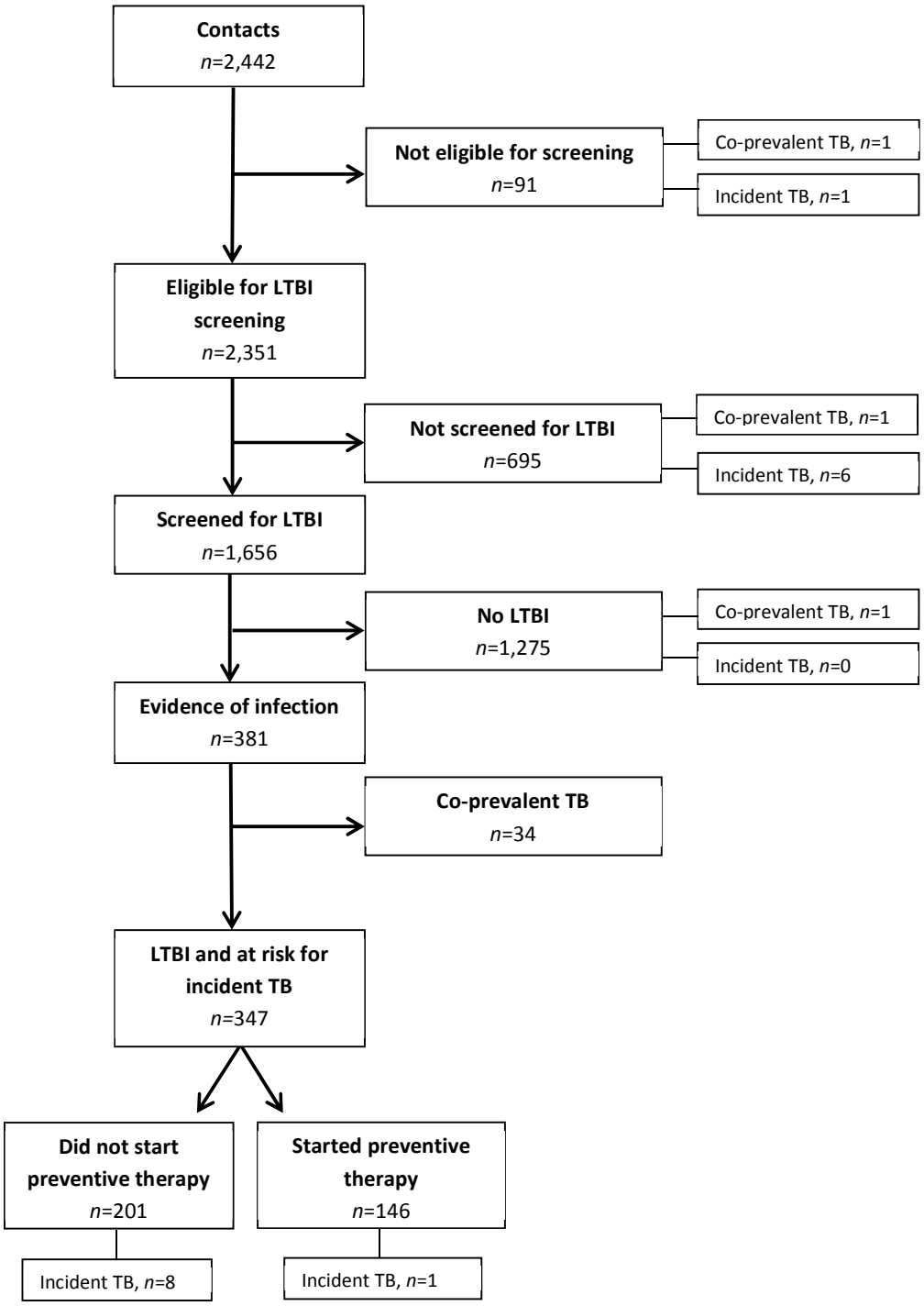
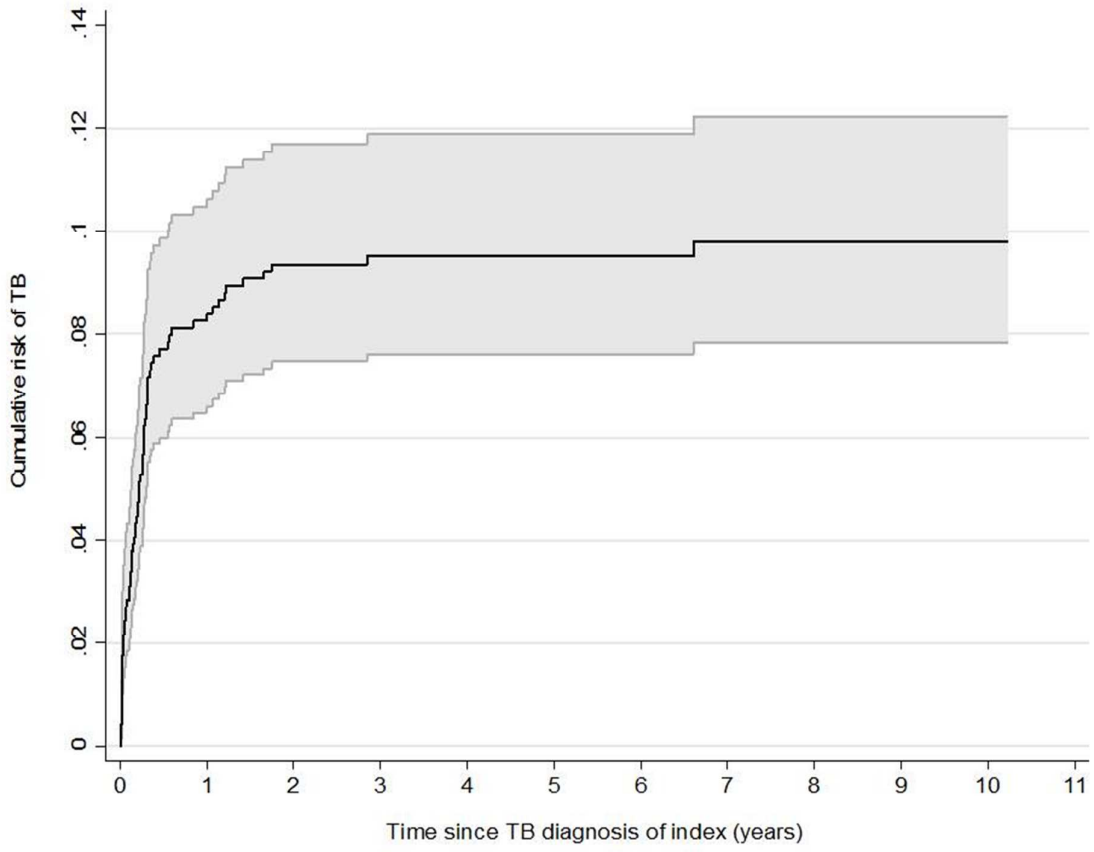


Figure 2.



	0-0.5	0.5-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11
At risk (n)	739	681	674	614	552	495	465	390	278	145	31	3
TB cases (n)	57	4	8	1	0	0	0	1	0	0	0	0

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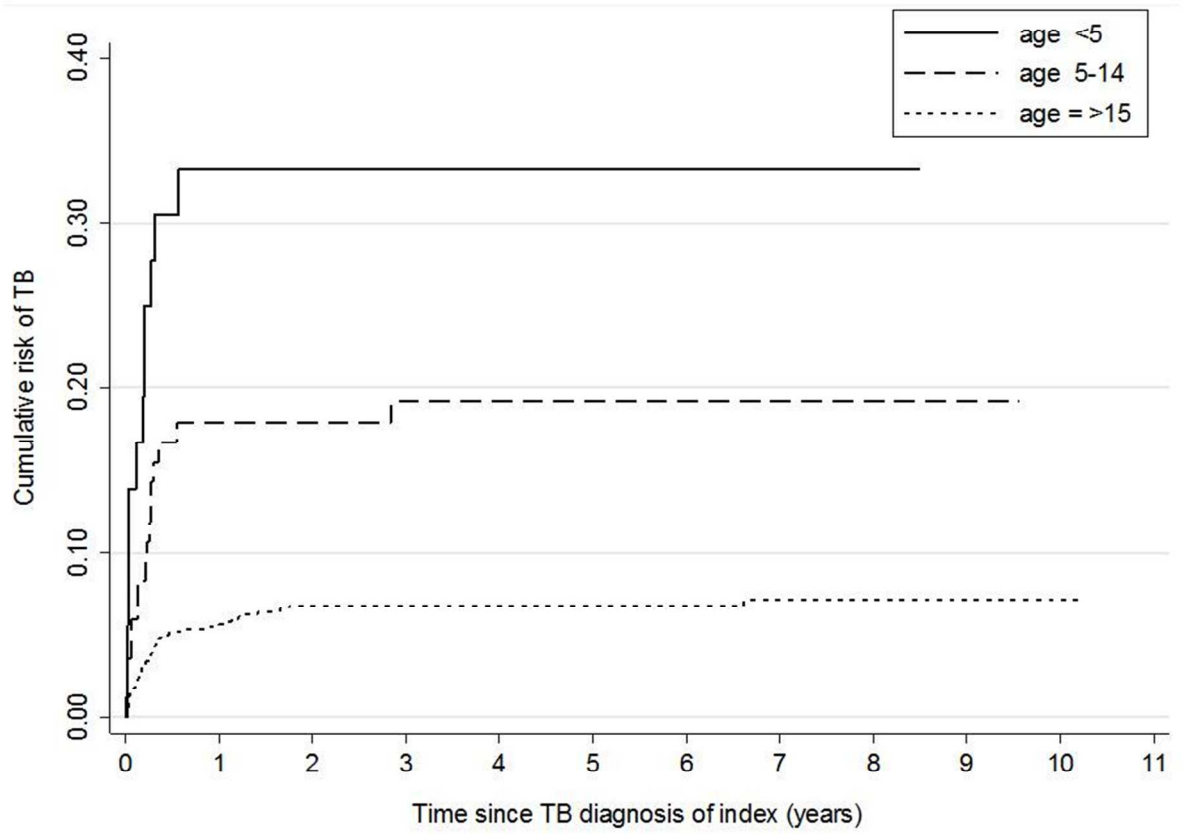
Figure 3.



Age (years)		0-0.5	0.5-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11
<5	At risk (n)	36	25	24	22	18	16	15	14	11	6		
	TB cases (n)	11	1	0	0	0	0	0	0	0	0		
5-14	At risk (n)	84	70	69	68	61	59	52	51	38	22	2	
	TB cases (n)	14	1	0	1	0	0	0	0	0	0	0	
≥15	At risk (n)	619	586	581	524	473	420	398	325	229	117	29	3
	TB cases (n)	32	2	8	0	0	0	0	1	0	0	0	0