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Immigrant screening for latent tuberculosis infection – numbers needed to test and treat: A Norwegian population-based study

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ABSTRACT

Objectives Explore the effectiveness of the Norwegian immigrant LTBI screening programme by estimating numbers needed to screen (NNS) and treat (NNT) to prevent one tuberculosis (TB) case, and measure the effect of timely follow-up of screening results.

Design Population-based prospective study

Participants Immigrants to Norway

Outcome Incident TB

Methods We obtained aggregated data on immigration to Norway in 2008-2011 and used data from the Norwegian Surveillance System for Infectious Diseases to assess the number of TB cases arising in this cohort within 5 years after arrival. We calculated average NNSs and NNTs for immigrants from the top 10 source countries for TB in Norway and by estimated TB incidence rates (IRs) in source countries. We explored the sensitivity of these estimates regarding test sensitivity, treatment efficacy, and treatment adherence using an extreme value approach, and assessed the effects of emigration, time to TB diagnosis (to define incident TB), and intervention timing.

Results
NNSs and NNTs were overall high, with substantial variation. The NNT showed numerically stronger negative correlation with the TB notification rate in Norway [-0.75 (95% CI -1.05 to -0.44)] than with the World Health Organisation IR [-0.32 (95% CI -0.93 to 0.29)]. NNTs were affected substantially by emigration and the definition of incident TB. Estimates were lowest for Somali [NNS 99 (70-150), NNT 27 (19-41)] and highest for Thai immigrants [NNS 585 (413-887), NNT 111 (79-116)]. Implementing LTBI treatment in immigrants sooner after arrival may improve the effectiveness of the programme.

Conclusions
Using TB notifications in Norway, rather than IR in source countries, would improve targeting of immigrants for LTBI management. However, the overall high NNT is a concern and challenges the scale-up of preventive LTBI treatment for significant public-health impact. Better data are urgently needed to monitor and evaluate NNS and NNT in countries implementing LTBI screening.

Strengths and limitations of this study

- We were able to demonstrate the effect of timing of interventions, as we had information on time in Norway prior to tuberculosis (TB) diagnosis or latent tuberculosis infection (LTBI) treatment.
- We could assess the effect of emigration on our estimates because aggregated national migration data at the country level were available.
- The screening coverage in Norway is high among asylum seekers and refugees, but less known in other groups.
- The currently weak monitoring and evaluation systems of the LTBI screening programme limit access to individual data to provide information on yield and programme effectiveness.
- From register data, we could not clearly disentangle those who were ill on arrival (co-prevalent TB) from cases that were potentially preventable through LTBI management (incident TB).

BACKGROUND

The World Health Organisation (WHO) have issued guidelines for the programmatic management of latent tuberculosis infection (LTBI).[1 2] The guidelines strongly recommend screening for and treatment of LTBI in groups at high-risk groups for tuberculosis (TB) and conditionally in recent immigrants from high- to low TB incidence countries.[1 2] LTBI is common and the risk of progression to TB varies substantially among individuals, assumed to reflect age, time since infection, and host immune status.[1]

The identification of target immigrant groups for LTBI management remains challenging in most low-TB incidence settings. There has been a call for the harmonisation of migrant screening policies across Europe.[3] Eligibility for screening is commonly based on the TB IR in the country of origin or the reason for immigration, with typical focus on asylum seekers and refugees.[3] It has, however, been suggested that the targeting of immigrants based on the TB IR in the host country may improve the effectiveness of immigrant screening programmes.[4]

In Norway, foreign-born individuals account for almost 90% of TB notifications and the majority are diagnosed in the first 5 years after arrival.[5] Based on molecular surveillance of *Mycobacterium tuberculosis* strains, the majority of TB in the foreign-born population is assumed to reflect reactivation of LTBI acquired prior to arrival.[5] Against this backdrop, Norway has a well-established immigrant screening programme for TB and LTBI. Immigrants are currently targeted for TB screening based on the WHO-estimated TB incidence rates (IRs) in their countries of birth.[6] Immigrants younger than 35 years are also targeted for LTBI management to prevent future development of TB. The eligibility for arrival LTBI screening has differed over time; in March 2017 the IR cut-off value was changed from >40/100,000 to >200/100,000 (including immigrants from Afghanistan and Eritrea).[7] The monitoring and evaluation system of the long-standing TB and LTBI screening programme is weak.

The objective of this study was to use Norwegian immigration and TB surveillance data to measure the effectiveness of the immigrant LTBI screening programme, using estimates of the number needed to screen (NNS) and number needed to treat (NNT) for different immigrant screening strategies. We also assessed the impact of LTBI treatments in a 4-year cohort of immigrants to Norway, and measured the effect of timely follow-up of screening results.

METHODS

Data and sources

Administrative data on the number of immigrants by year, country of origin, and reason for immigration were obtained from the Norwegian Directorate of Immigration for newly arrived asylum seekers and from Statistics Norway for other immigrant groups. Country of origin reflected citizenship for asylum seekers and country of birth for other immigrant groups.

As later emigration from Norway is substantial in some immigrant groups, we obtained administrative data on individuals' time in Norway before emigration. For refugees and asylum seekers, these data were based on a percentile distribution of the number of days before final application rejection (by country); for other immigrant groups, it was based on aggregated data on the average time in Norway before emigration (by reason for immigration).

We used the WHO Global TB Report 2014 estimates of TB IR in countries of origin in 2013.[6] Demographic and clinical information about individuals with TB and LTBI treatment was obtained from the Norwegian Surveillance System for Infectious Diseases (MSIS). It is mandatory for laboratories and clinicians to report TB diagnosis and treatment, and prescription of LTBI treatment, to MSIS. Untreated LTBI is not reported. The sensitivity of MSIS data is assumed to be high because

notifications are sent from multiple sources and are checked routinely against TB drug prescriptions. On the MSIS notification form, clinicians report time in Norway prior to diagnosis for foreign-born individuals using the following categories: <1 month, 1-6 months, 7-12 months, 1-2 years, 3-4 years, 5-9 years, and ≥10 years.

We used all TB notifications to MSIS in 2008-2015 (year of reporting) to identify the top 10 source countries (in absolute numbers; appendix 1) for immigrant TB in Norway, and then calculated the TB notification rate (NR) in Norway based on the number of observation years, corrected for emigration (table 1).

Assumptions and definitions

We calculated the number of arriving immigrants aged < 35 years from the top 10 source countries for TB in Norway and for countries with WHO-estimated TB IRs > 150/100,000 population in the period 2008-2011.[6] A positive interferon-gamma release assay (IGRA) was used as a proxy for LTBI. The estimated percentage of immigrants with a positive IGRA was based on published literature, and ranged from 18% to 29%, depending on the WHO-estimated TB IR in the country of origin and the age group; 0-14 years and 15-35 years.[8-10]

We calculated the probability that a foreign-born patient notified to MSIS with TB in 2008-2015 was diagnosed with TB within the first 5 years after arrival (based on the date of clinical sample collection for TB diagnosis) and was aged < 40 years at diagnosis (eligible for screening on arrival and within 5 years). Within this relatively short time period, infection was considered to have occurred abroad prior to entry. Similar calculations were performed for LTBI treatment, based on the date of notification.

We then calculated the total number of individuals with TB or LTBI treatment by multiplying the number of patients by the adjusted probability that they immigrated to Norway in 2008-2011. When information about time since arrival was missing, we calculated the weighted probability of time since immigration separately for each country of origin, and corrected for missing data based on the country-specific distribution of this information.

We excluded individuals who were diagnosed with TB (based on the date of sample collection for TB diagnosis) within 1 month after arrival, as these individuals were most likely ill on arrival (co-prevalent TB) and TB would not be preventable through LTBI screening and treatment. For sensitivity analysis, we also excluded individuals who were notified within 1-6 months. These cases may or may not have been preventable through LTBI management. Based on this uncertainty, we present NNSs and NNTs separately for TB diagnosed >1 and >6 months after arrival, and applied these two definitions of incident TB throughout the study.

NNS and NNT

We estimated the NNS to prevent one incident TB case by calculating the ratio of the number of arriving immigrants to the number of incident TB cases observed in Norway within 5 years.

We estimated the crude NNT as the ratio of the number of individuals testing positive for LTBI to the number of incident TB cases observed in Norway. This NNT can be interpreted as a combined effect of emigration and TB risk. As emigration is substantial in some groups, we also estimated time in Norway before emigration and used this value to calculate corrected NNTs as 1/risk of preventable TB in the case of no emigration from Norway. This number can be interpreted as the TB risk corrected for the effect of migration (appendix 2).

We explored the sensitivity of these estimates regarding test sensitivity and treatment efficacy and adherence to treatment using an extreme value approach. IGRA sensitivity was estimated to be 84% (with 81% and 87% applied as extreme values),[11 12] and chemoprophylaxis efficacy was estimated to be 65% (50%-80%),[1 13] consistent with a UK study.[4] The rate of treatment

adherence was estimated to be 90% (80%-100%), according to published[14-16] and unpublished Norwegian data. The number of incident TB cases was adjusted accordingly and defined as preventable TB (table 2).

We then explored correlation with 95% confidence intervals (CIs) of the NNT with the TB NR in Norway and WHO-estimated TB IR.

Prevented TB and timing of LTBI treatment

We calculated the expected number of incident TB cases prevented by the LTBI treatments during the study period by multiplying the number of LTBI treatments by the subsequent risk of preventable TB in different time periods (based on MSIS data). The calculations were limited to the first 5 years in Norway (e.g. if a person received LTBI treatment after 4 years in Norway, LTBI treatment would have a preventive effect for only 1 year). We assumed that a person did not leave Norway after receiving LTBI treatment, and assumptions were based on incident TB > 1 month after arrival. We calculated the percentage increase in prevented TB (potential for additional prevention) when LTBI treatment was initiated within the first (i) 6 months and (ii) 12 months after arrival to Norway (based on the 84% sensitivity/65% treatment effectiveness/90% adherence estimates and incident TB > 1 month after arrival). The outcome reflects a combination of the times of TB diagnosis and LTBI treatment, or a strong effect of one of them.

Patient and Public Involvement

Patients and or the public were not involved in the study

RESULTS

The majority of foreign-born TB patients in Norway originated from the Horn of Africa; Somalia alone accounted for 44% of TB cases from the top 10 source countries (table 1). Overall, a high proportion of TB occurred within the first year after arrival, with some variation among source countries. The fraction of observation years lost due to emigration was substantial in some groups and varied among source countries (table 1).

Most immigrants from the Horn of Africa, Afghanistan, and Myanmar arrived as refugees and asylum seekers (figure 1). Most immigrants from Vietnam, Thailand, and Pakistan arrived for family reunification, whereas immigrants from India arrived for family reunification and work, and the majority of immigrants from the Philippines came to work as au-pairs.

> Insert figure 1 about here <

Overall, estimated NNSs and NNTs were high (table 2). Estimates were lowest for Somalia: screening of 70-105 and treatment of 14-28 Somali immigrants was required to prevent one incident TB case. Estimates were lowest when we corrected for the effect of emigration and applied the 1-month threshold to define incident TB (table 2). The same pattern was seen for all countries. NNTs were highest for immigrants from Pakistan and Thailand, although NNSs were substantially higher for Thailand. For most source countries, the number of preventable TB cases was reduced by one-third when the 6-month definition of incident TB was applied compared with the 1-month definition, but with variation (range 16%-75%).

We found a stronger numerical correlation between the TB NR in Norway and NNT to prevent one incident TB case [correlation coefficient (CC) -0.75 (95% CI -1.05 to -0.44)] than between the NNT and WHO-estimated IR in the country of origin [CC -0.32 (95% CI -0.93 to 0.29)] for the top 10 source countries for TB in Norway (using corrected NNTs and the 6-month definition of incident TB). The CCs were affected only modestly by emigration and definition of incident TB, and unaffected

by the extreme value approach (data not shown). The WHO-estimated TB IRs in Somalia and Pakistan in 2013 were similar (274 and 270/100,000 person-years). These values contrast with our findings that NNTs were lowest for Somali immigrants and among the highest for Pakistani immigrants. The WHO-estimated TB IR in the Philippines is high, and the NNSs and NNTs were high in our setting. NNTs for immigrants from Pakistan and Thailand were similar, although the estimated TB IR is substantially lower in Thailand than in Pakistan. When eligibility for screening was based on TB IRs in countries of origin, NNTs were fairly similar for the different thresholds and highest for those with IRs > 200/100,000, including Eritrea and Afghanistan. Estimates were lowest for immigrants from the Horn of Africa.

Only a small percentage (range 3% - 21%) of LTBI-positive immigrants were estimated to have received LTBI treatment (table 3). The resulting estimated number of incident TB cases prevented by LTBI treatment was therefore modest, with a limited overall public-health impact of the immigrant LTBI screening programme in Norway in this period.

Almost half (range 30%-58%) of LTBI treatments were prescribed >12 months after arrival in Norway (table 3). The highest percentages were for immigrants from the Horn of Africa, where most incident TB occurs. A substantial proportion of additional incident TB cases could have been prevented if the same number of LTBI treatments had been prescribed sooner after arrival (table 3).

Table 1 TB and LTBI among immigrants aged < 35 years arriving in Norway in 2008-2011 by country of origin. (Only top ten source countries for TB in Norway listed by country).

Country of origin (WHO estimated annual TB incidence rate per 100,000)[a]	Arrivals in Norway in 2008-2011[b] (<35 years)	Estimated no. of LTBI cases[c]	Notified TB in Norway first 5 years after arrival (<40 years)		Time in Norway prior to TB diagnosis (months)				TB within 12 m after arrival	Person-years under observation[e]	Observation years lost due to emigration[f]
					< 1	1–6	7–12	13–60			
	(n)	(n)	(n)	NR[d]	(n)	(n)	(n)	(n)	(%)	(n)	(proportion)
By country											
Myanmar (369)	900	255	18	419	1	7	4	6	67	4300	0.06
Philippines (288)	6700	1909	64	358	1	29	14	20	69	17,900	0.47
Somalia (274)	7400	2019	252	900	23	74	54	101	60	28,000	0.25
Pakistan (270)	2000	520	12	174	0	3	2	7	42	6900	0.29
Ethiopia (207)	2400	651	46	667	5	8	9	24	48	6900	0.42
Afghanistan (189)	6800	1417	44	238	4	10	7	23	48	18,500	0.46
Thailand (171)	3900	776	20	120	1	6	2	11	45	16,600	0.14
India (167)	2800	682	18	167	1	3	2	12	28	10,800	0.23
Vietnam (140)	900	177	12	364	0	9	1	2	83	3300	0.25
Eritrea (78)	6900	1888	82	307	10	21	15	36	56	26,700	0.22
Horn of Africa[g]	16,700	4558	418	679	38	141	78	161	61	61,600	0.26
Countries grouped by estimated TB incidence rate [a]											
>150/100,000	37,100	7058	533	446	43	161	104	225	58	119,400	0.36
>200/100,000	23,300	5485	428	595	35	137	87	169	61	72,000	0.38
>200/100,000 incl[h]	37,000	8692	554	473	49	167	110	228	59	117,200	0.37

TB, tuberculosis; NR, notification rate per 100,000 person years under observation; LTBI, latent tuberculosis infection.

[a] From the 2014 World Health Organisation Global tuberculosis control report.[6]

[b] Number of immigrants, rounded to the nearest hundred. Data were obtained from Statistics Norway and the Norwegian Directorate of Immigration.

[c] Interferon-gamma release assay positivity was used as a proxy for LTBI (estimates are based on published data).

[d] Based on estimated total number of person years under observation.

[e] Adjusted according to estimated time in Norway before emigration for immigrants arriving in Norway in 2008-2011.

[f] Estimated proportion observation years lost due to emigration within the first 5 years after arrival

[g] Including Somalia, Eritrea, and Ethiopia.

[h] Includes countries with TB IRs > 200/100,000 and Eritrea and Afghanistan (in line with current Norwegian guidelines).

Table 2 Estimated numbers of preventable TB cases and the numbers of immigrants needed to screen (NNS) and to treat (NNT) for latent tuberculosis infection to prevent one case of tuberculosis in the first five years after arrival, among immigrants arriving in Norway 2008-2011.

Country of origin (WHO estimated TB incidence rate per 100,000)[a]	Incident TB based on diagnosis ≥ 1 month after arrival				Incident TB based on diagnosis > 6 months after arrival			
	Preventable TB[b]	NNS[c, d]	NNT, crude[c,e]	NNT, corrected[c,f]	Preventable TB[c]	NNS[c]	NNT, crude[c,e]	NNT, corrected[c,f]
By country								
Myanmar (369)	8 (12–6)	111 (78–168)	30 (22–46)	na*	5 (7–3)	181 (128–274)	50 (35–76)	*na
Philippines (288)	31 (44–20)	218 (154–330)	62 (44–94)	59 (42–89)	16 (23–11)	419 (296–635)	119 (84–180)	104 (74–158)
Somalia (274)	113 (159–74)	66 (47–100)	18 (13–27)	13 (10–20)	75 (107–50)	99 (70–150)	27 (19–41)	17 (12–26)
Pakistan (270)	6 (9–4)	319 (225–484)	85 (60–129)	75 (53–113)	4 (6–3)	440 (311–668)	117 (83–178)	94(67–143)
Ethiopia (207)	20 (29–13)	118 (83–179)	32 (23–49)	23 (16–34)	16 (22–10)	152 (108–231)	42 (29–63)	26 (19–40)
Afghanistan (189)	20 (28–13)	347 (245–526)	72 (51–109)	46 (32–69)	15 (22–10)	444 (313–673)	92 (65–140)	54 (38–82)
Thailand (171)	9 (13–6)	414 (292–628)	83 (59–126)	78 (55–119)	7 (9–4)	585 (413–887)	117 (83–178)	111 (79–169)
India (167)	8 (12–6)	334 (236–506)	82 (58–124)	75 (53–113)	7 (10–5)	396 (279–600)	97 (68–147)	89 (63–135)
Vietnam (140)	6 (8–4)	151 (107–229)	30 (21–46)	28 (20–42)	1 (2–1)	605 (427–917)	120 (85–182)	93 (66–141)
Eritrea (78)	35 (50–23)	194 (137–295)	53 (38–81)	43 (31–65)	24 (34–16)	286 (202–433)	78 (55–119)	56 (40–85)
Horn of Africa[g]	168 (238–111)	99 (70–151)	26 (18–39)	14 (10–21)	115 (163–76)	145 (103–220)	38 (27–58)	16 (12–25)
Countries grouped by estimated TB incidence rate [a]								
>150/100,000	241 (341–159)	154 (109–234)	32 (23–49)	23 (16–35)	160 (226–105)	232 (164–352)	48 (34–73)	30 (21–45)
>200/100,000	193 (274–127)	121 (85–183)	28 (20–43)	20 (15–31)	124 (175–82)	188 (133–286)	44 (31–67)	27 (19–41)
>200/100,00 incl[h]	248 (351–164)	149 (105–226)	35 (25–53)	23 (16–34)	163 (231–108)	227 (160–344)	53 (38–81)	29 (20–43)

Estimates include TB occurring after 1 and 6 months and within the first 5 years following arrival in Norway, 2008-2011.

TB, tuberculosis; NNS and NNT, numbers needed to screen and treat to prevent one incident TB case within the first 5 years after arrival.

*Emigration is minimal (na) since the majority arrived as refugees under the United Nations High Commissioner for Refugees and were granted residency prior to arrival

[a] From the 2014 World Health Organisation Global tuberculosis control report.[6]

[b] Number of TB patients notified from screening cohorts, adjusted regarding diagnostic test sensitivity, treatment efficacy, and adherence.

[c] Using the point estimate with (range) of sensitivity, efficacy, and adherence estimates.

[d] Ratio of the number of new arrivals to the number of preventable TB cases observed in Norway.

[e] Ratio of the number of latent tuberculosis infection and preventable TB cases observed in Norway, i.e. combined effect of emigration and risk of TB.

[f] 1 / risk of preventable TB for a person who stayed in Norway for 5 years, i.e. corrected for the effect of emigration.

[g] Including Somalia, Eritrea, and Ethiopia.

[h] Includes countries with TB IRs > 200/100,000 and Eritrea and Afghanistan (in line with current Norwegian guidelines).

Table 3 Estimated numbers of tuberculosis cases prevented by latent tuberculosis infection treatment of immigrants during the first 5 years after arrival in Norway, 2008-2011.

Country of origin (WHO estimated TB incidence rate per 100,000)[a]	TB notification (<40 years)	LTBI treatment (<40 years)[b]	Time of LTBI treatment after arrival (months)			LTBI treatment > 12 m after arrival	Number of incident TB cases prevented by LTBI treatment (range)[c]	Additional preventable incident TB cases if all LTBI treatments were initiated within 6 or 12 months after arrival	
			≤6	7-12	13-60				
	(n)	(n, %)	(n)	(n)	(n)	(%)	(n)	6 months (%)	12 months (%)
By country									
Myanmar (369)	18	54 (21)	23	15	16	30	3 (4–2)	21	9
Philippines (288)	64	200 (10)	61	68	71	35	2 (3–1)	57	11
Somalia (274)	252	391 (19)	64	113	215	55	19 (27–13)	38	15
Pakistan (270)	12	16 (3)	4	4	9	52	0.2 (0.2–0.1)	22	7
Ethiopia (207)	46	108 (17)	13	37	58	54	3 (5–2)	15	8
Afghanistan (189)	44	159 (11)	32	54	74	46	3 (4–2)	18	7
Thailand (171)	20	53 (7)	13	15	25	47	0.5 (0.7–0.3)	30	4
India (167)	18	21 (3)	6	8	7	33	0.2 (0.3–0.2)	10	2
Vietnam (140)	12	26 (15)	8	10	8	32	0.5 (0.6–0.3)	99	4
Eritrea (78)	82	195 (10)	21	60	113	58	3 (6–2)	42	16
Horn of Africa[d]	380	694 (15)	98	210	386	56	36 (50–24)	23	11
Countries grouped by estimated TB incidence rate [a]									
>150/100,000	533	1193 (17)	267	381	545	46	36 (51–24)	30	10
>200/100,000	428	900 (16)	198	288	414	46	30 (42–20)	34	12
>200/100,000 incl[e]	554	1252 (14)	250	402	600	48	39 (55–26)	29	11

TB, tuberculosis; LTBI, latent tuberculosis infection; m, months

[a] From the 2014 World Health Organisation Global tuberculosis control report.[6]

[b] Number and percentage of LTBI positive persons with LTBI treatment.

[c] Highest and lowest estimates using the point estimate with (range) of diagnostic test sensitivity, treatment efficacy, and adherence estimates.

[d] Including Somalia, Eritrea, and Ethiopia.

[e] Includes countries with TB IRs > 200/100,000 and Eritrea and Afghanistan (in line with current Norwegian guidelines).

DISCUSSION

The NNS and NNT to prevent one adverse outcome are measures used to communicate the effectiveness of health care interventions.[17] In this study of the immigrant LTBI screening programme in Norway, we found overall very high NNSs and NNTs to prevent one incident TB case, and higher than in a previous studies.[4 18] Screening based on the TB NR in Norway rather than the TB IRs in source countries improved targeting of immigrants for LTBI management. However, NNSs and NNTs remained high for most countries by either approach, even when we applied the most optimistic estimates for test sensitivity, treatment effectiveness, and treatment adherence.

Strengths and limitations

The strengths of this study include the availability of detailed country-specific administrative immigration and emigration data, the high sensitivity of the TB and LTBI surveillance system, and the performance of comprehensive sensitivity analyses for the different estimates. Given the availability of information on time in Norway prior to TB diagnosis or LTBI treatment from MSIS, we were able to demonstrate the effect of intervention timing. This approach has important clinical implications. Lastly, the overall consistency with the UK study[4] makes comparison possible.

Study limitations include the currently weak monitoring and evaluation system of the Norwegian LTBI screening programme. Multiple service providers are involved in the screening process, with no harmonisation of data collection or follow-up documentation. Substantial delays in the provision of government-issued personal ID numbers to recent immigrants, specifically asylum seekers, have compromised follow-up and data linkage. For the same reason, we could not calculate NNTs based on absolute risk reduction in LTBI-treated individuals.

Screening coverage is high among asylum seekers and refugees, but less known for other immigrant groups (family reunification, students and immigrant workers). If screening participation was non-selective, it would not affect our estimates. However, if the prevalence of LTBI differed among those screened and not screened, our estimates may be biased.

Norwegian guidelines encourage treatment of individuals at greatest risk of progression to TB. If LTBI-positive individuals prescribed LTBI treatment were at greater risk than untreated LTBI-positive individuals, we may have underestimated the number of incident TB cases prevented by LTBI treatment during the study period. We may also have underestimated the overall impact of the screening programme, as incident TB occurring >5 years after arrival was not included. However, whether incident TB occurring several years after arrival is related to initial infection or subsequent re-infection is difficult to evaluate in long-term follow-up studies. A Dutch study of molecular data in contacts showed that 83% of incident cases occurred within 5 years of the source case and >95% occurred within 10 years,[19] suggesting that the degree of potential underestimation was modest. Finally, the effects of screening for TB and LTBI are difficult to disentangle, as they contribute to each other.

Comparison with other studies

A UK study documented substantial variation in NNSs and NNTs among immigrants from the 10 most commonly reported source countries for TB in the UK.[4] The figures contrasted with estimated TB IRs in the source countries. Similarly, we found great variation in NNSs and NNTs, which were not consistently related to estimated WHO TB IRs in source countries. Immigrants may originate from specific geographical areas with higher or lower rates than national averages, and their socio-economic circumstances before and after arrival in host countries may differ. Surprisingly, the estimated NNTs for source countries were considerably higher in Norway than in the UK. In the current study, we differentiated between co-prevalent and incident TB and accounted for

emigration; both factors have profound impacts on NNTs and were not assessed in the UK study.[6] Immigrants are screened soon after arrival in Norway, and many leave the country before the end of the 5-year observation period. In contrast, the UK study examined long-term immigrants. Differences in TB epidemiology may also contribute to the observed differences. The UK researchers reported higher TB rates, and therefore also higher transmission rates, than in most Western European countries, specifically in larger cities.[20] The higher estimates for treatment adherence in this study compared with the UK study would narrow, rather than widen, the difference in NNTs.

A mathematical modelling study from Australia found that a combination of screening and subsequent treatment of all LTBI positive immigrants would result in an overall reduction in number of TB cases of about one-third to one-half from 2013 - 2050.[18] The NNSs were 297 for all immigrants and 136 for immigrants originating from countries with an estimated TB IR >100/100 000, which is somewhat lower than in the current study. As in the UK study the model was based on permanent arrivals.

Challenges of NNS/NNT estimation in immigrant screening

The lifetime age-weighted risk of TB following infection in settings with low exogenous re-infection is estimated to be 12%.[21] The reported low pooled positive predictive value of the IGRA (2.7%) corresponds to an NNT of 37 across different settings and populations.[22] This corresponds to 111 months of treatment to prevent one TB case in need of 6 months of treatment. Thus, the risk reduction following LTBI treatment must be large to reduce the NNT. Although morbidity, mortality, and transmission can be avoided if TB is prevented, the benefit of LTBI treatment for the individual should outweigh the risk of severe adverse effects. Although LTBI treatment is safe overall, it carries a risk of severe and potentially life-threatening toxic adverse effects.[23]

Register data did not allow us to clearly distinguish co-prevalent TB from TB that developed later and was potentially preventable through LTBI management (incident TB). LTBI is considered to comprise a spectrum of infection states.[24] A prolonged asymptomatic phase of early subclinical TB may precede clinical presentation with active disease.[25 26] A pre- and post-arrival evaluation of a cohort of US immigrants reported that >80% of TB cases diagnosed within 1 year of receiving pre-arrival examination represented co-prevalent TB.[26] TB diagnosed <1 month after arrival is clearly not preventable, whereas TB diagnosis within 1-6 months may or may not be preventable. Based on this uncertainty, we presented NNSs and NNTs separately for TB diagnosed >1 and >6 months after arrival.

Emigration was substantial in some groups. Immigrants to Norway from Myanmar were almost exclusively refugees under the United Nations High Commissioner for Refugees and were granted residency prior to arrival, whereas applications from adult asylum seekers from Afghanistan commonly were rejected. The observation years lost due to emigration were also substantial in other groups with high proportions of asylum seekers. Immigrants from the Philippines often arrive as au-pairs and are granted only 2-year work permits. Emigration may also lead to NNT overestimation if immigrants who show LTBI positivity on screening upon arrival in Norway develop TB after emigration.

The effect of timeliness of screening and treatment

In this study, fewer than one in five estimated LTBI-positive individuals (if all immigrants were screened) was treated. This gap in the *intention to screen is intention to treat* principle represents a challenge and has been reported in other Norwegian studies;[27 28] it has been due partly to Norwegian guidelines (in which the groups targeted for screening has been wider than those targeted for treatment), and measures have been taken to minimise it.[7] It may, however, also signal that the

number of LTBI-positive individuals is too high for the health services to treat, and/or that clinicians are reluctant to initiate LTBI treatment in individuals with unknown risk of progression to disease.

As a high proportion of incident TB cases occur early after arrival, an important component to improve the impact of the screening programme would be to ensure expedited follow-up and LTBI treatment initiation. The reduced risk of progression to TB over time will increase NNT estimates with time, and delayed follow-up represents missed opportunities. The potential for additional prevented cases varied across countries of origin. The high potential for additional prevention among immigrants from Vietnam reflects the high proportions of those who are ill early after arrival and those for whom LTBI treatment is initiated late, whereas the opposite was observed for India.

Public health implications

The overall high NNSs and NNTs in this study call into question whether routine LTBI screening of immigrants in a high-income low-incidence country is feasible, safe and effective, without the application of additional selection criteria. Although LTBI management based on TB notification in Norway rather than WHO estimated IRs in countries of origin would have improved the targeting of immigrants, the NNSs and NNTs remained high. This is in line with a recently published systematic review on the effectiveness of LTBI screening among migrants in the EU/EEA, in which the authors conclude that the effectiveness of LTBI programmes is limited due to the large pool of immigrants with LTBI, suboptimal diagnostic tests and weak care cascade, and that high screening uptake and treatment completion will ensure greatest benefit on both the individual and the public health level.[29]

The estimated number of incident TB cases prevented by LTBI treatment was modest suggesting that substantial scale-up of the LTBI care cascade is necessary to strengthen the public health impact. Until new tests with higher predictive values for TB are available,[23] there are two complementary approaches to reduce the NNSs and NNTs. Firstly, screening could be limited to immigrants with additional risk factors for disease, such as young age, recent known contact, abnormal x-ray findings, and immunosuppressive conditions. This approach, however, will require additional resources to correctly identify risk groups on entry. Secondly, the LTBI care cascade could be improved so that further examinations and treatment are offered sooner following a positive LTBI screening test. The programme has the potential to prevent additional TB cases if more immigrants with LTBI are offered treatment, and this treatment starts sooner after arrival.

Monitoring of the effectiveness of screening should urgently be improved. The data in Norway are better than in many other countries, but still with wide uncertainty. As immigration trends and composition and health services vary considerably among countries, better monitoring and evaluation of current screening programmes are needed so that countries can adjust their policies based on the yield of screening.

Even when applying the most optimistic estimates regarding diagnostic test sensitivity, treatment efficacy, and adherence to treatment, a substantial proportion of incident TB cases will not be prevented through LTBI screening and management. Easy and equitable access to health care services for all should remain a cornerstone of tuberculosis control and prevention so that clinial cases are detected and treated early.

Ethical approval

Ethical approval of the study was obtained from Regional Committee for Medical and Health Research Ethics, south east Norway (2017/164).

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Competing interests statement

None declared.

Authors' contributions

BAW initiated the study, and BAW and EH wrote the protocol. BAW, RW, and GMG were responsible for modelling and analyses; BAW, RW and EH drafted the manuscript; and BAW, PA, PAA, EH, RW, and GMG provided input to discussions. All authors have read and approved the final version of the manuscript.

Data sharing statement

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Figure legends

Figure 1 Reasons for immigration for immigrants aged < 35 years arriving in Norway in 2008-2011, by country of origin (%).

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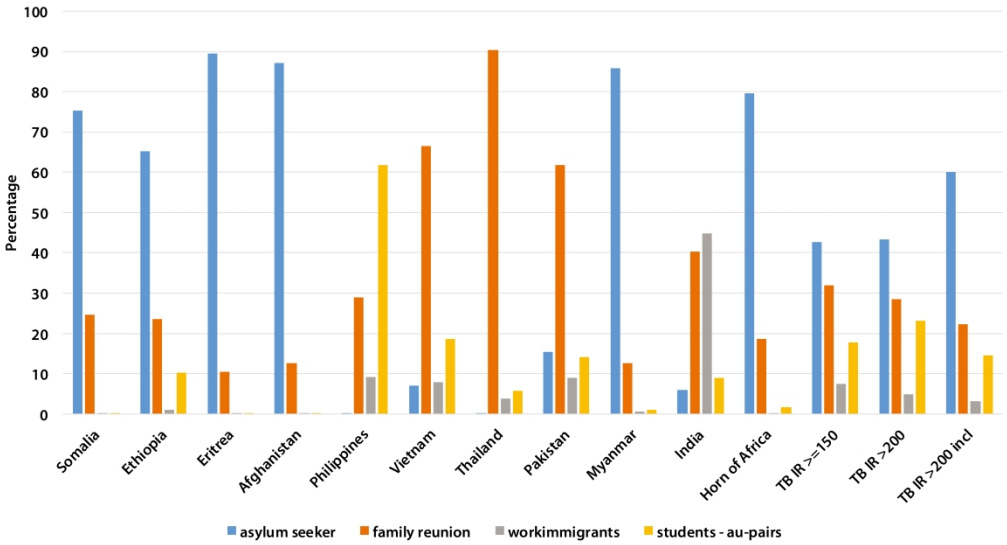

Figure 1 Reasons for immigration for immigrants aged < 35 years arriving in Norway in 2008-2011, by country of origin (%).

Appendix 1. Number of notified TB cases from the top ten source countries for immigrant TB in Norway, 2008-2015 (Source: MSIS*)

Countries	2008	2009	2010	2011	2012	2013	2014	2015	Total
Somalia	70	106	72	106	112	102	84	47	699
Eritrea	12	24	16	20	23	41	47	49	232
Philippines	20	14	25	23	30	25	26	25	188
Pakistan	20	18	23	20	15	18	15	8	137
Ethiopia	9	27	17	14	15	16	17	15	130
Afghanistan	7	10	19	16	11	18	11	26	118
Thailand	10	16	15	10	11	8	14	13	97
Vietnam	10	15	12	11	7	15	12	7	89
India	7	9	7	4	11	12	9	6	65
Myanmar	11	6	10	8	7	7	3	2	54

MSIS, Norwegian Surveillance System for Infectious Diseases

Appendix 2. Estimates of number of immigrants eligible for screening, distribution of age and time in Norway and data sources

Information	Estimates	Sources
Immigrants eligible for screening (<35 yrs on arrival) Percentage of eligible immigrants aged 0-14 and 15-34 years	**Refugees**: 83% < 35 yrs. Among them 18% were 0-14 years and 82% were 15-34 years. **Family-reunion**: 80% < 35 years, among them 44% were 0-14 years and 56% were 15-34 yrs. **Work immigrants**: 70%, among them all were 15-34 yrs. **Students and au-pairs**: 95% < 35 years, among them all were 15-34 years	UDI[I] for refugees SSB[II] age distribution of immigrants in 2014 by reason for immigration
Adjusted observation time based on emigration for refugees	**Refugees**: percentile distribution of time before final rejection of application for residency **Other immigrant groups**: Aggregated data based on reason for immigration **Family reunion**: each individual contributes on average 4.5 observation years out of 5, equals 90% under observation for scaled arrivals **Work immigrants**: contributes on average 4.2 observation years out of 5, equals 84% under observation for scaled arrivals **Students and au-pairs**: contributes on average 1,74 observation years out of 5, equals 35% under observation for scaled arrivals	UDI[I] for refugees and SSB[II] for the remaining immigrant groups

[I] *UDI, Norwegian Directorate of Immigration*

[II] *SSB, Statistics Norway*

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Immigrant screening for latent tuberculosis infection – numbers needed to test and treat: A Norwegian population-based cohort study

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Immigrant screening for latent tuberculosis infection – numbers needed to test and treat: A Norwegian population-based cohort study

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ABSTRACT

Objectives Estimate the numbers needed to screen (NNS) and treat (NNT) to prevent one tuberculosis (TB) case in the Norwegian immigrant LTBI screening programme, and to explore the effect of delay of LTBI treatment initiation.

Design Population-based prospective cohort study

Participants Immigrants to Norway

Outcome Incident TB

Methods We obtained aggregated data on immigration to Norway in 2008-2011 and used data from the Norwegian Surveillance System for Infectious Diseases to assess the number of TB cases arising in this cohort within 5 years after arrival. We calculated average NNSs and NNTs for immigrants from the top 10 source countries for TB in Norway and by estimated TB incidence rates (IRs) in source countries. We explored the sensitivity of these estimates regarding test performance, treatment efficacy, and treatment adherence using an extreme value approach, and assessed the effects of emigration, time to TB diagnosis (to define incident TB), and intervention timing.

Results
NNSs and NNTs were overall high, with substantial variation. The NNT showed numerically stronger negative correlation with the TB notification rate in Norway [-0.75 (95% CI 1.00 to -0.44)] than with the World Health Organisation IR [-0.32 (95% CI -0.93 to 0.29)]. NNTs were affected substantially by emigration and the definition of incident TB. Estimates were lowest for Somali [NNS 99 (70-150), NNT 27 (19-41)] and highest for Thai immigrants [NNS 585 (413-887), NNT 117 (83-178)]. Implementing LTBI treatment in immigrants sooner after arrival may improve the effectiveness of the programme.

Conclusions
Using TB notifications in Norway, rather than IR in source countries, would improve targeting of immigrants for LTBI management. However, the overall high NNT is a concern and challenges the scale-up of preventive LTBI treatment for significant public-health impact. Better data are urgently needed to monitor and evaluate NNS and NNT in countries implementing LTBI screening.

Strengths and limitations of this study

- The study benefitted from access to high quality national data over several years, including immigration and surveillance data, allowing for calculation of group and country specific emigration numbers, providing a strong estimate of the person-time observation for recent immigrants.
- The way in which we constructed our dataset allowed for the inclusion of high quality data from multiple sources. With this, we were able to investigate the effect of LTBI treatment initiation within the first six versus 12 months after arrival.
- A methodological strength is that, through the extreme value approach, we include the results under a variety of estimates for LTBI test sensitivity, treatment efficacy and adherence to treatment.
- Our calculations relied on the proportion of individuals testing positive with IGRA (proxy for LTBI), which was based on published literature rather than individual data. This may bias our results in either direction.
- From register data, we could not clearly disentangle those who were ill on arrival (co-prevalent TB) from cases that were potentially preventable through LTBI management (incident TB).

BACKGROUND

The World Health Organisation (WHO) have issued guidelines for the programmatic management of latent tuberculosis infection (LTBI).[1 2] The guidelines strongly recommend screening for and treatment of LTBI in groups at high-risk for tuberculosis (TB) and conditionally in recent immigrants from high- to low TB incidence countries.[1] LTBI is common and the risk of progression to TB varies substantially among individuals, assumed to reflect age, time since infection, and host immune status.[1]

The identification of target immigrant groups for LTBI management remains challenging in most low-TB incidence settings. There has been a call for the harmonisation of migrant screening policies across Europe.[3] Eligibility for screening is commonly based on the TB IR in the country of origin or the reason for immigration, with typical focus on asylum seekers and refugees.[3] It has, however, been suggested that the targeting of immigrants based on the TB IR in the host country may improve the effectiveness of immigrant screening programmes.[4]

In Norway, foreign-born individuals account for almost 90% of TB notifications and the majority are diagnosed in the first 5 years after arrival.[5] Based on molecular surveillance of *Mycobacterium tuberculosis* strains, the majority of TB in the foreign-born population is assumed to reflect reactivation of LTBI acquired prior to arrival.[5] Against this backdrop, Norway has a well-established immigrant screening programme for TB and LTBI. Immigrants are currently targeted for TB screening based on the WHO-estimated TB incidence rates (IRs) in their countries of birth.[6] Immigrants younger than 35 years are also targeted for LTBI management to prevent future development of TB. The eligibility for arrival LTBI screening has differed over time; in March 2017 the IR cut-off value was changed from >40/100,000 to >200/100,000 (including immigrants from Afghanistan and Eritrea).[7] The monitoring and evaluation system of the long-standing TB and LTBI screening programme is weak.

The primary objective of this study was to use aggregated numbers of Norwegian immigration and individual level TB surveillance data to estimate the of number needed to screen (NNS) and number needed to treat (NNT) with LTBI chemoprophylaxis to prevent one TB case in the immigrant LTBI screening programme. Secondary objectives were to estimate the number of TB cases prevented by the current strategy in a 4-year cohort of immigrants, and to explore the effect of delay of LTBI treatment initiation within the first 6 months versus the 12 months after arrival, using the same immigration and surveillance data.

METHODS

Data sources and creation of data set for modelling and analysis

We combined aggregate numbers from Norwegian immigration data (i.e. information on the entire cohort) and individual level TB surveillance data (i.e. information on individuals with TB or LTBI treatment) to create a unified dataset for modelling and analysis. All steps are described in the text below. A complete overview is also presented in table format in appendices 1a-d.

Data and sources

Immigration and emigration data

We have used administrative data on immigration by year, country of origin, and reason for immigration in Norway in 2008-2011. Data were obtained separately from two different sources: the Norwegian Directorate of Immigration (UDI) for newly arrived asylum seekers and from Statistics Norway (SSB) for other immigrant groups. The number of immigrants is based on number of asylum applications and

number of residence permits for other immigrant groups. Country of origin reflects citizenship for asylum seekers and country of birth for other immigrant groups. We estimated the proportion aged <15 years and 15-35 years by country, reason for immigration and year of immigration based on the reported age-distribution from SSB/UDI (appendix 1a). As emigration from Norway is substantial in some immigrant groups, we obtained aggregated administrative data on time spent in Norway before emigration from the same sources (further described below). In the model, we have assumed that immigrants who received residence permit or applied for asylum actually immigrated to Norway and that immigrants who were later registered as emigrated, or had a final rejection of application for asylum, actually emigrated (appendix 1c).

TB cases and LTBI treatment

For individuals with TB and LTBI treatment (i.e. the people of interest), individual-level demographic and clinical information was obtained from the Norwegian Surveillance System for Infectious Diseases (MSIS) for the years 2008-2016. This time-period allows for five years observation time for all immigrants. The information included age at notification, country of birth, date of notification, date of diagnosis (collection of clinical sample) and date of start of treatment. Further, on the MSIS notification form, clinicians report time in Norway prior to diagnosis for foreign-born individuals using the following categories: <1 month, 1-6 months, 7-12 months, 1-2 years, 3-4 years, 5-9 years, and >10 years. Date of arrival is not reported.

It is mandatory for laboratories and clinicians to report TB diagnosis and treatment outcome, and prescription of LTBI treatment, to MSIS. Untreated LTBI is not reported. The sensitivity of MSIS data is assumed to be high because notifications are sent from multiple sources and are checked routinely against TB drug prescriptions.

We used all TB notifications to MSIS in 2008-2015 (year of reporting) to identify the top 10 source countries (in absolute numbers; appendix 2) for immigrant TB in Norway and then calculated the TB notification rate (NR) in Norway based on the number of observation years.

Construction of analysis dataset

Based on the aggregated immigration data we calculated the number of arriving immigrants aged ≤ 35 years from the top 10 source countries for TB in Norway and for countries with WHO-estimated TB IRs > 150/100,000 population in the period 2008-2011.[6] We used the WHO Global TB Report 2014 estimates of TB IR in countries of origin in 2013.[6]

Estimated prevalence of LTBI

We used a positive IGRA as a proxy for LTBI. The prevalence of IGRA positives was based on published literature, including Norwegian data on asylum seekers,[8] and ranged from 18% to 29%, depending on the WHO-estimated TB IR in the country of origin and the age group; 0-14 years and 15-35 years.[8-10] The number of immigrants with LTBI in the model was estimated by multiplying the number of arriving immigrants with the published estimates of IGRA positives, separately for the two age-groups. In the model, we have assumed that the age- and country specific prevalence of LTBI from published literature, including Norwegian data, is a fair proxy for the LTBI prevalence in the arrival cohort.

TB and LTBI treatments in the 2008-2011 immigrant cohort

We used the categorical information about time in Norway prior to diagnosis from MSIS to estimate a probability distribution for each case's arrival year in Norway (e.g. "a case received a diagnosis in December 2010 and has been in Norway for <1 month, therefore they have 100% probability that they arrived in Norway in 2010 and belong to the 2008-2011 immigrant cohort", "a case received a diagnosis in March 2012 and has been in Norway for 1-6 months, therefore they have a 50% probability that they arrived in Norway in 2011, and 50% probability that they arrived in Norway in 2012"). When information about time since arrival was missing, we imputed this information by applying the country-specific probability distribution for time-in-Norway. We then estimated the number of individuals with TB or LTBI treatment who belonged to the 2008-2011 cohort of immigrants by multiplying the number of cases by the probability that they immigrated to Norway in 2008-2011.

We excluded individuals who were diagnosed with TB (based on the date of sample collection for TB diagnosis) within 1 month after arrival, as these individuals were most likely ill on arrival (co-prevalent TB) and TB would not be preventable through LTBI screening and treatment. For sensitivity analysis, we also excluded individuals who were notified within 1-6 months. These cases may or may not have been preventable through LTBI management. Based on this uncertainty, we present NNSs and NNTs separately for TB diagnosed >1 and >6 months after arrival, and applied these two definitions of incident TB throughout the study.

Estimation of time in Norway

Since emigration is substantial in some immigrant groups, we estimated the cumulative probability of time under observation in Norway based on UDI/SSB administrative data. For asylum seekers, data on emigration was obtained as percentile distributions of number of days from application date to date of final rejection of application, e.g. among 421 asylum seekers from Somalia who arrived in Norway in 2008 and whose application for asylum later was rejected, 10% were rejected within 62 days, 20% were rejected within 87 days and so on up until the 90% percentile. We used this information to calculate the number of person-years of observation lost due to emigration within the first five years after arrival in Norway. This was done separately by country, TB IR in country of citizenship and by year.

For other immigrant groups, data on emigration was based on aggregated September 2014 data, containing the number of immigrants per year and the number of them that emigrated before September 2014 (separately by reason for immigration). See Table 1 for an example of the data and the formulae used to estimate the cumulative probability distribution for duration of time in Norway for the cohort.

Table 1. The cumulative probability distribution for duration of time in Norway for immigrants other than asylum seekers.

Year of arrival (X)	Number arrived in year X	Number emigrated before 09/2014	Average time in Norway as of 09/2014	cumulative proportion staying in Norway as of 09/2014
2008	D1	N1	6,25	1-N1/D1
2009	D2	N2	5,25	1-N2/D2
2010	D3	N3	4,25	1-N3/D3
2011	D4	N4	3,25	1-N4/D4

Finalizing dataset

Using the prior pieces of information (number of people arriving each year, probability distribution of time to emigration, and for each TB/LTBI diagnosis – time since immigration and estimated year of arrival) we created a dataset containing yearly cohorts of people who immigrated to Norway between 2008 and 2011 and are followed up for either five years or until they emigrate from Norway (the shorter of the two).

Outcomes

Preventable TB/Risk of preventable TB

We defined preventable TB as a patient notified with TB to MSIS and who: (i) arrived to Norway in 2008-2011, (ii) was notified to MSIS > 1 month (6 months) and < 5 years after arrival, (iii) was younger than 40 years of age at notification (to allow for five years observation time after screening). With this relatively short time period, we assume that they were infected prior to arrival in Norway. We explored the sensitivity of these estimates regarding test performance, treatment efficacy and adherence to treatment using an extreme value approach. IGRA sensitivity was estimated to be 84% (with 81% and 87% applied as extreme values)[11 12] and chemoprophylaxis efficacy was estimated to be 65% (50%-80%),[1 13] consistent with a UK study.[4] The rate of treatment adherence was estimated to be 90% (80%-100%), according to published[14-16] and unpublished Norwegian data. The number of incident TB cases was adjusted accordingly and defined as preventable TB (table 2). We excluded TB cases that were on TB treatment on arrival to Norway.

For each time period after arrival to Norway (<1 month, 1-6 months, 7-12 months, 1-2 years, 3-4 years, 5-9 years, and >10 years) we obtained the number of preventable TB cases and then calculated the risk of preventable TB per time period (i.e. number of cases divided by number of people). The risk of developing TB during this time period was then also converted into monthly risk using the formula 1-(1-totalrisk)^(1/number-months).

NNS and NNT

We estimated the NNS to prevent one incident TB case by calculating the ratio of the number of arriving immigrants to the number of preventable TB cases observed in Norway within 5 years. We used the extreme value approach to explore the sensitivity of these estimates.

We estimated the *crude NNT* as the ratio of the number of individuals testing positive for LTBI to the number of preventable TB cases. This NNT can be interpreted as a combined effect of emigration and TB risk (i.e. if someone emigrates from Norway they cannot receive a TB diagnosis in Norway, thus the more emigration the lower the risk for TB observed in Norway). We used the information on person years lost for observation due to emigration to calculate *corrected NNT* as 1/(risk of preventable TB in 5 years). This number can be interpreted as the NNT if all immigrants remained in Norway for 5 years.

We then explored correlation with 95% confidence intervals (CIs) of the NNT with the TB NR in Norway and WHO-estimated TB IR. The purpose of this analysis was to identify which data source (TB NR in Norway or WHO-estimated TB IR) had a stronger association with public health implications in Norway (NNT).

Prevented TB due to LTBI treatment and the effect delay of LTBI treatment initiation

We estimated the expected number of TB prevented by the LTBI treatments provided during the study period. This was calculated by multiplying the number of LTBI treatments by the subsequent risk of

preventable TB in different time-periods (based on the categorical MSIS data on time since arrival). The calculations were limited to the first 5 years in Norway (e.g. if a person received LTBI treatment after 4 years in Norway, LTBI treatment would have a preventive effect for only 1 year). In the model, we have assumed that all immigrants eligible for screening actually were screened and that they were screened soon after arrival in line with the mandatory screening programme. We further assumed that a person did not leave Norway after receiving LTBI treatment. Calculations were based on incident TB > 1 month after arrival.

We calculated the percentage increase in prevented TB (potential for additional prevention) when LTBI treatment was initiated within the first (i) 6 months and (ii) 12 months after arrival to Norway (based on the 84% sensitivity/65% treatment effectiveness/90% adherence estimates and incident TB > 1 month after arrival) through multiplying increased number of people screened by sensitivity by effectiveness by adherence. The outcome reflects a combination of the timing of TB diagnosis and LTBI treatment, or a strong effect of one of them.

Uncertainty in the calculations

None of the calculations in this study included uncertainty. Our model was primarily deterministic. The source of uncertainty in our study came from running our deterministic model with alternative IGRA sensitivities and treatment efficacies (the extreme value approach).

Patient and Public Involvement

Patients and or the public were not involved in the study

RESULTS

The majority of foreign-born TB patients in Norway originated from the Horn of Africa; Somalia alone accounted for 44% of TB cases from the top 10 source countries (table 2). Overall, a high proportion of TB occurred within the first year after arrival, with some variation among source countries. The fraction of observation years lost due to emigration was substantial in some groups and varied among source countries (table 2).

Most immigrants from the Horn of Africa, Afghanistan, and Myanmar arrived as refugees and asylum seekers (figure 1). Most immigrants from Vietnam, Thailand, and Pakistan arrived for family reunification, whereas immigrants from India arrived for family reunification and work, and the majority of immigrants from the Philippines came to work as au-pairs.

> Insert figure 1 about here <

Overall, estimated NNSs and NNTs were high (table 3). Estimates were lowest for Somalia: screening of 70-150 and treatment of 19-41 Somali immigrants was required to prevent one incident TB case (6 months threshold for preventable TB). NNTs were lowest for estimates corrected for the effect of emigration and with the 1-month threshold to define incident TB, compared to the crude NNT and the 6 months threshold (table 3). The same pattern was seen for all countries. NNTs were highest for immigrants from Pakistan and Thailand, although NNSs were substantially higher for Thailand. For most source countries, the number of preventable TB cases was reduced by one-third when the 6-month definition of incident TB was applied compared with the 1-month definition, but with variation (range 16%-75%).

We found a stronger numerical correlation between the TB NR in Norway and NNT to prevent one incident TB case [correlation coefficient (CC) -0.75 (95% CI -1.00 to -0.44)] than between the NNT and WHO-estimated IR in the country of origin [CC -0.32 (95% CI -0.93 to 0.29)] for the top 10 source countries for TB in Norway (using corrected NNTs and the 6-month definition of incident TB). The CCs were affected only modestly by emigration and definition of incident TB, and unaffected by the extreme value approach (data not shown). The WHO-estimated TB IRs in Somalia and Pakistan in 2013 were similar (274 and 270/100,000 person-years). These values contrast with our findings that NNTs were lowest for Somali immigrants and among the highest for Pakistani immigrants. The WHO-estimated TB IR in the Philippines is high, and the NNSs and NNTs were high in our setting. NNTs for immigrants from Pakistan and Thailand were similar, although the estimated TB IR is substantially lower in Thailand than in Pakistan. When eligibility for screening was based on TB IRs in countries of origin, NNTs were fairly similar for the different thresholds and highest for those with IRs > 200/100,000, including Eritrea and Afghanistan. Estimates were lowest for immigrants from the Horn of Africa.

Only a small percentage (range 3% - 21%) of LTBI-positive immigrants were estimated to have received LTBI treatment (table 4). The resulting estimated number of incident TB cases prevented by LTBI treatment was therefore modest, with a limited overall public-health impact of the immigrant LTBI screening programme in Norway in this period.

Almost half (range 30%-58%) of LTBI treatments were prescribed >12 months after arrival in Norway (table 4). The highest percentages were for immigrants from the Horn of Africa, where most incident TB occurs. A substantial proportion of additional incident TB cases could have been prevented if the same number of LTBI treatments had been prescribed sooner after arrival (table 4).

Table 2 TB and LTBI among immigrants aged < 35 years arriving in Norway in 2008-2011 by country of origin. (Only to ten source countries for TB in Norway listed by country).

Country of origin (WHO estimated annual TB incidence rate per 100,000)[a]	Arrivals in Norway in 2008-2011[b] (<35 years)	Estimated no. of LTBI cases[c]	Notified TB in Norway first 5 years after arrival (<40 years)		Time in Norway prior to TB diagnosis (months)				TB within 12 m after arrival	Person-years under observation[d]	Observation years lost due to emigration[e]
					< 1	1–6	7–12	13–60			
	(n)	(n)	(n)	NR	(n)	(n)	(n)	(n)	(%)	(n)	(proportion)
By country											
Myanmar (369)	900	255	18	419	1	7	4	6	67	4300	0.06
Philippines (288)	6700	1909	64	358	1	29	14	20	69	17,900	0.47
Somalia (274)	7400	2019	252	900	23	74	54	101	60	28,000	0.25
Pakistan (270)	2000	520	12	174	0	3	2	7	42	6900	0.29
Ethiopia (207)	2400	651	46	667	5	8	9	24	48	6900	0.42
Afghanistan (189)	6800	1417	44	238	4	10	7	23	48	18,500	0.46
Thailand (171)	3900	776	20	120	1	6	2	11	45	16,600	0.14
India (167)	2800	682	18	167	1	3	2	12	28	10,800	0.23
Vietnam (140)	900	177	12	364	0	9	1	2	83	3300	0.25
Eritrea (78)	6900	1888	82	307	10	21	15	36	56	26,700	0.22
Horn of Africa[f]	*16,700*	*4558*	*380*	*679*	*38*	*103*	*78*	*161*	*58*	*61,700*	*0.26*
Countries grouped by estimated TB incidence rate[a]											
>150/100,000	37,100	7058	533	446	43	161	104	225	58	119,400	0.36
>200/100,000	23,300	5485	428	595	35	137	87	169	61	72,000	0.38
>200/100,000 incl[g]	37,000	8692	554	473	49	167	110	228	59	117,200	0.37

TB, tuberculosis; NR, notification rate per 100,000 person years under observation; LTBI, latent tuberculosis infection.

[a] From the 2014 World Health Organisation Global tuberculosis control report.[6]

[b] Number of immigrants, rounded to the nearest hundred. Data were obtained from Statistics Norway and the Norwegian Directorate of Immigration.

[c] Interferon-gamma release assay positivity was used as a proxy for LTBI (estimates are based on published data, including Norwegian data).

[d] Adjusted according to estimated time in Norway before emigration for immigrants arriving in Norway in 2008-2011.

[e] Estimated proportion observation years lost due to emigration within the first 5 years after arrival

[f] Including Somalia, Eritrea, and Ethiopia.

[g] Includes countries with TB IRs > 200/100,000 and Eritrea and Afghanistan (in line with current Norwegian guidelines)

Table 3 Estimated numbers of preventable TB cases and the numbers of immigrants needed to screen (NNS) and to treat (NNT) for latent tuberculosis infection to prevent one case of tuberculosis in the first five years after arrival, among immigrants arriving in Norway 2008-2011.

Country of origin (WHO estimated TB incidence rate per 100,000)[a]	Incident TB based on diagnosis ≥ 1 month after arrival				Incident TB based on diagnosis > 6 months after arrival			
	Preventable TB[b,c]	NNS[c,d]	NNT, crude[c,e]	NNT, corrected[c,f]	Preventable TB[b,c]	NNS[c,d]	NNT, crude[c,e]	NNT, corrected[c,f]
By country								
Myanmar (369)	8 (12–6)	111 (78–168)	30 (22–46)	na*	5 (7–3)	181 (128–274)	50 (35–76)	*na
Philippines (288)	31 (44–20)	218 (154–330)	62 (44–94)	59 (42–89)	16 (23–11)	419 (296–635)	119 (84–180)	104 (74–158)
Somalia (274)	113 (159–74)	66 (47–100)	18 (13–27)	13 (10–20)	75 (107–50)	99 (70–150)	27 (19–41)	17 (12–26)
Pakistan (270)	6 (9–4)	319 (225–484)	85 (60–129)	75 (53–113)	4 (6–3)	440 (311–668)	117 (83–178)	94(67–143)
Ethiopia (207)	20 (29–13)	118 (83–179)	32 (23–49)	23 (16–34)	16 (22–10)	152 (108–231)	42 (29–63)	26 (19–40)
Afghanistan (189)	20 (28–13)	347 (245–526)	72 (51–109)	46 (32–69)	15 (22–10)	444 (313–673)	92 (65–140)	54 (38–82)
Thailand (171)	9 (13–6)	414 (292–628)	83 (59–126)	78 (55–119)	7 (9–4)	585 (413–887)	117 (83–178)	111 (79–169)
India (167)	8 (12–6)	334 (236–506)	82 (58–124)	75 (53–113)	7 (10–5)	396 (279–600)	97 (68–147)	89 (63–135)
Vietnam (140)	6 (8–4)	151 (107–229)	30 (21–46)	28 (20–42)	1 (2–1)	605 (427–917)	120 (85–182)	93 (66–141)
Eritrea (78)	35 (50–23)	194 (137–295)	53 (38–81)	43 (31–65)	24 (34–16)	286 (202–433)	78 (55–119)	56 (40–85)
Horn of Africa[g]	*168 (238–111)*	*99 (70–151)*	*27 (19–41)*	*15 (11–23)*	*115 (163–76)*	*145 (103–220)*	*40 (28–60)*	*18 (13–27)*
Countries grouped by estimated TB incidence rate [a]								
>150/100,000	241 (341–159)	154 (109–234)	32 (23–49)	23 (16–35)	160 (226–105)	232 (164–352)	48 (34–73)	30 (21–45)
>200/100,000	193 (274–127)	121 (85–183)	28 (20–43)	20 (15–31)	124 (175–82)	188 (133–286)	44 (31–67)	27 (19–41)
>200/100,00 incl[h]	248 (351–164)	149 (105–226)	35 (25–53)	23 (16–34)	163 (231–108)	227 (160–344)	53 (38–81)	29 (20–43)

Estimates include TB occurring after 1 and 6 months and within the first 5 years following arrival in Norway, 2008-2011.

TB, tuberculosis; NNS and NNT, numbers needed to screen and treat to prevent one incident TB case within the first 5 years after arrival.

*Emigration is minimal (na) since the majority arrived as refugees under the United Nations High Commissioner for Refugees and were granted residency prior to arrival

[a] From the 2014 World Health Organisation Global tuberculosis control report.[6]

[b] Number of TB patients notified from screening cohorts, adjusted regarding diagnostic test sensitivity, treatment efficacy, and adherence.

[c] Using the point estimate with (range) of sensitivity, efficacy, and adherence estimates.

[d] Ratio of the number of new arrivals to the number of preventable TB cases observed in Norway.

[e] Ratio of the number of latent tuberculosis infection and preventable TB cases observed in Norway, i.e. combined effect of emigration and risk of TB.

[f] 1 / risk of preventable TB for a person who stayed in Norway for 5 years, i.e. corrected for the effect of emigration.

[g] Including Somalia, Eritrea, and Ethiopia.

[h] Includes countries with TB IRs > 200/100,000 and Eritrea and Afghanistan (in line with current Norwegian guidelines).

Table 4 Estimated numbers of tuberculosis cases prevented by latent tuberculosis infection treatment of immigrants during the first 5 years after arrival in Norway, 2008-2011.

Country of origin (WHO estimated TB incidence rate per 100,000)[a]	TB notification (<40 years)	LTBI treatment (<40 years)[b]	Time of LTBI treatment after arrival (months)			LTBI treatment > 12 m after arrival	Number of incident TB cases prevented by LTBI treatment (range)[c]	Additional preventable incident TB cases if all LTBI treatments were initiated within 6 or 12 months after arrival	
			≤6	7-12	13-60				
	(n)	(n, %)	(n)	(n)	(n)	(%)	(n)	6 months (%)	12 months (%)
By country									
Myanmar (369)	18	54 (21)	23	15	16	30	3 (4–2)	21	9
Phil4ppines (288)	64	200 (10)	61	68	71	35	2 (3–1)	57	11
Somalia (274)	252	391 (19)	64	113	215	55	19 (27–13)	38	15
Pakistan (270)	12	16 (3)	4	4	9	52	0.2 (0.2–0.1)	22	7
Ethiopia (207)	46	108 (17)	13	37	58	54	3 (5–2)	15	8
Afghanistan (189)	44	159 (11)	32	54	74	46	3 (4–2)	18	7
Thailand (171)	20	53 (7)	13	15	25	47	0.5 (0.7–0.3)	30	4
India (167)	18	21 (3)	6	8	7	33	0.2 (0.3–0.2)	10	2
Vietnam (140)	12	26 (15)	8	10	8	32	0.5 (0.6–0.3)	99	4
Eritrea (78)	82	195 (10)	21	60	113	58	3 (6–2)	42	16
Horn of Africa[d]	*380*	*694 (15)*	*98*	*210*	*386*	*56*	*32 (45–21)*	*25*	*12*
Countries grouped by estimated TB incidence rate [a]									
>150/100,000	533	1193 (17)	267	381	545	46	36 (51–24)	30	10
>200/100,000	428	900 (16)	198	288	414	46	30 (42–20)	34	12
>200/100,000 incl[e]	554	1252 (14)	250	402	600	48	39 (55–26)	29	11

TB, tuberculosis; LTBI, latent tuberculosis infection

[a] From the 2014 World Health Organisation Global tuberculosis control report.[6]

[b] Percentage of LTBI positive persons with LTBI treatment.

[c] Highest and lowest estimates using the point estimate with (range) of sensitivity, efficacy, and adherence estimates.

[d] Including Somalia, Eritrea, and Ethiopia.

[e] Includes countries with TB IRs > 200/100,000 and Eritrea and Afghanistan (in line with current Norwegian guidelines).

DISCUSSION

The NNS and NNT to prevent one adverse outcome are measures used to communicate the effectiveness of health care interventions.[11] In this study of the immigrant LTBI screening programme in Norway, we found overall very high NNSs and NNTs to prevent one incident TB case, and higher than in a previous studies.[4 12] Screening based on the TB NR in Norway rather than the TB IRs in source countries improved targeting of immigrants for LTBI management. However, NNSs and NNTs remained high for most countries by either approach, even when we applied the most optimistic estimates for test sensitivity, treatment effectiveness, and treatment adherence.

Strengths and limitations

The strengths of this study include the availability of detailed country-specific administrative immigration and emigration data that provides a strong estimate of the person-time observation for recent immigrants, the high sensitivity of the TB and LTBI surveillance system, and the performance of comprehensive sensitivity analyses for the different estimates. Given the availability of information on time in Norway prior to TB diagnosis or LTBI treatment from MSIS, we were able to demonstrate the effect of intervention timing. This approach has important clinical implications. Lastly, the overall consistency with the UK study[4] makes comparison possible.

Study limitations include the currently weak monitoring and evaluation system of the Norwegian LTBI screening programme. Multiple service providers are involved in the screening process, with no harmonisation of data collection or follow-up documentation. Substantial delays in the provision of government-issued personal ID numbers to recent immigrants, specifically asylum seekers, have compromised follow-up and data linkage. For the same reason, we could not calculate NNTs based on absolute risk reduction in LTBI-treated individuals. The lack of denominator data is a common challenge in most countries, which renders immigrant screening programmes poorly evaluated. We have used comprehensive administrative data and high-coverage surveillance data including information on LTBI treatment, to overcome these limitations.

Screening coverage is high among asylum seekers and refugees, but less known for other immigrant groups (family reunification, students and immigrant workers). If screening participation was non-selective, it would not affect our estimates. However, if the prevalence of LTBI differed among those screened and not screened, our estimates may be biased.

The prevalence of LTBI in the arriving immigrant cohort was based on published literature, including Norwegian data on asylum seekers. [8-10] Whether these correctly reflects the prevalence of LTBI in the arriving cohort is unknown and this may potentially have biased our estimates in either direction. If the LTBI prevalence in the arriving immigrants was lower than estimated, the reported NNSs and NNTs would be too high, whereas with a higher prevalence than estimated our NNSs and NNTs would be too low.

Norwegian guidelines encourage treatment of individuals at greatest risk of progression to TB. If LTBI-positive individuals prescribed LTBI treatment were at greater risk than untreated LTBI-positive individuals, we may have underestimated the number of TB cases prevented by LTBI treatment during the study period. We may also have underestimated the overall benefit of the screening programme, as incident TB occurring >5 years after arrival was not included. However, whether incident TB occurring several years after arrival is related to initial infection or subsequent re-infection is difficult to evaluate in long-term follow-up studies. A Dutch study of molecular data in contacts showed that 83% of incident cases occurred within 5 years of the source case and >95% occurred within 10 years,[13] suggesting that

the degree of potential underestimation was modest. Finally, the effects of screening for TB and LTBI are difficult to disentangle, as they contribute to each other.

Comparison with other studies

A UK study documented substantial variation in NNSs and NNTs among immigrants from the 10 most commonly reported source countries for TB in the UK.[4] The figures contrasted with estimated TB IRs in the source countries. Similarly, we found great variation in NNSs and NNTs, which were not consistently related to estimated WHO TB IRs in source countries. Immigrants may originate from specific geographical areas with higher or lower rates than national averages, and their socio-economic circumstances before and after arrival in host countries may differ. Surprisingly, the estimated NNTs for source countries were overall considerably higher in Norway than in the UK. NNTs for immigrants from Pakistan were 85 (60-129) and 34 (17-70), from Somalia 18 (13-27) and 4 (1-7) and from India 82 (58-124) and 37 (20-61) in Norway and UK respectively.[4] In the current study, we differentiated between co-prevalent and incident TB and accounted for emigration; both factors have profound impacts on NNTs and were not assessed in the UK study.[6] Immigrants are screened soon after arrival in Norway, and many leave the country before the end of the 5-year observation period. In contrast, the UK study examined long-term immigrants. Differences in TB epidemiology may also contribute to the observed differences. The UK researchers reported higher TB rates, and therefore also higher transmission rates, than in most Western European countries, specifically in larger cities.[14] The higher estimates for treatment adherence in this study compared with the UK study would narrow, rather than widen, the difference in NNTs. A mathematical modelling study from Australia found that a combination of screening and subsequent treatment of all LTBI positive immigrants would result in an overall reduction in number of TB cases of about one-third to one-half from 2013 - 2050.[12] The NNSs were 297 for all immigrants and 136 for immigrants originating from countries with an estimated TB IR >100/100 000, which is somewhat lower than in the current study. As in the UK study the model was based on permanent arrivals.

Challenges of NNS/NNT estimation in immigrant screening

The lifetime age-weighted risk of TB following infection in settings with low exogenous re-infection is estimated to be 12%.[15] The reported low pooled positive predictive value of the IGRA (2.7%) corresponds to an NNT of 37 across different settings and populations.[16] This corresponds to 111 months of treatment to prevent one TB case in need of 6 months of treatment. Thus, the risk reduction following LTBI treatment must be large to reduce the NNT. Although morbidity, mortality, and transmission can be avoided if TB is prevented, the benefit of LTBI treatment for the individual should outweigh the risk of severe adverse effects. Although LTBI treatment is safe overall, it carries a risk of severe and potentially life-threatening toxic adverse effects.[17]

Register data did not allow us to clearly distinguish co-prevalent TB from TB that developed later and was potentially preventable through LTBI management (incident TB). LTBI is considered to comprise a spectrum of infection states.[18] A prolonged asymptomatic phase of early subclinical TB may precede clinical presentation with active disease.[19 20] A pre- and post-arrival evaluation of a cohort of US immigrants reported that >80% of TB cases diagnosed within 1 year of receiving pre-arrival examination represented co-prevalent TB.[20] TB diagnosed <1 month after arrival is clearly not preventable, whereas TB diagnosis within 1-6 months may or may not be preventable. Based on this uncertainty, we presented NNSs and NNTs separately for TB diagnosed >1 and >6 months after arrival.

Emigration was substantial in some groups. Immigrants to Norway from Myanmar were almost exclusively refugees under the United Nations High Commissioner for Refugees and were granted residency prior to arrival, whereas applications from adult asylum seekers from Afghanistan commonly were rejected. The observation years lost due to emigration were also substantial in other groups with high proportions of asylum seekers. Immigrants from the Philippines often arrive as au-pairs and are granted only 2-year work permits. Emigration may also lead to NNT overestimation if immigrants who show LTBI positivity on screening upon arrival in Norway develop TB after emigration.

The effect of timeliness of screening and treatment

In this study, less than one in five estimated LTBI-positive individuals (if all immigrants were screened) was treated. This gap in the *intention to screen is intention to treat* principle represents a challenge and has been reported in other Norwegian studies;[21-23] it has been due partly to Norwegian guidelines (in which the groups targeted for screening has been wider than those targeted for treatment), and measures have been taken to minimise it.[7] It may, however, also signal that the number of LTBI-positive individuals is too high for the health services to treat, and/or that clinicians are reluctant to initiate LTBI treatment in individuals with unknown risk of progression to disease.

As a high proportion of incident TB cases occur early after arrival, an important component to improve the impact of the screening programme would be to ensure expedited follow-up and LTBI treatment initiation. Increased attention is given to the need for timely interventions as the incubation period for TB. [24] The reduced risk of progression to TB over time will increase NNT estimates with time, and delayed follow-up represents missed opportunities. The potential for additional prevented cases varied across countries of origin. The high potential for additional prevention among immigrants from Vietnam reflects the high proportions of those who are ill early after arrival and those for whom LTBI treatment is initiated late, whereas the opposite was observed for India.

Comparing NNT to TB NR in Norway and WHO estimated IRs in countries of origin

We found a stronger numerical correlation between the NNT and TB NR in Norway than between the NNT and WHO-estimated IR in the country of origin for the top 10 source countries for TB in Norway. This is expected, as both the NRs and the NNT estimates are derived from the same Norwegian data (representing the same subset of the population who immigrated to Norway, which may not be a representative sample of the people in the country of origin), whereas the WHO-estimated IRs use country-specific data to make representative estimates for their national populations. When a large difference exists between the people in the country of origin and the subset of the population who immigrated to Norway, we would expect the TB NR in Norway to be more programmatically useful than the WHO estimated IRs in countries of origin.

Public health implications

The overall high NNSs and NNTs in this study call into question whether routine LTBI screening of immigrants in a high-income low-incidence country is feasible, safe and effective, without the application of additional selection criteria. Although LTBI management based on TB notification in Norway rather than WHO estimated IRs in countries of origin, would have improved the targeting of immigrants, the NNSs and NNTs remained high.

The estimated number of incident TB cases prevented by LTBI treatment was modest suggesting that substantial scale-up of the LTBI care cascade is necessary to strengthen the public health impact.

Until new tests with higher predictive values for TB are available,[23] there are two complementary approaches to reduce the NNSs and NNTs. Firstly, screening could be limited to immigrants with additional risk factors for disease, such as young age, recent known contact, abnormal x-ray findings, and immunosuppressive conditions. This approach, however, will require additional resources to correctly identify risk groups on entry. Secondly, the LTBI care cascade could be improved so that further examinations and treatment are offered sooner following a positive LTBI screening test. The programme has the potential to prevent additional TB cases if more immigrants with LTBI are offered treatment, and this treatment starts sooner after arrival. TB disease develops usually 3-9 months after exposure and rarely more than two years after exposure,[24] which strengthens the recommendation for prompt follow-up of immigrant screening. A combination of these two approaches seems most plausible. Cost-effectiveness studies could help to identify the most beneficial approach in a Norwegian setting.

Monitoring of the effectiveness of screening should urgently be improved, by targeting immigrants with risk factors in addition to the TB IR in the source country and ensuring timely follow-up of screening. The data in Norway are better than in many other countries, but still with wide uncertainty. As immigration trends and composition and health services vary considerably among countries, better monitoring and evaluation of current screening programmes are needed so that countries can adjust their policies based on the yield of screening.

Even when applying the most optimistic estimates regarding diagnostic test sensitivity, treatment efficacy, and adherence to treatment, a substantial proportion of incident TB cases will not be prevented through LTBI screening and management. Easy and equitable access to health care services for all should remain a cornerstone of tuberculosis control and prevention so that clinical cases are detected and treated early.

Ethical approval

Ethical approval of the study was obtained from Regional Committee for Medical and Health Research Ethics, south east Norway (2017/164).

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Competing interests statement

None declared.

Authors' contributions

BAW initiated the study, and BAW and EH wrote the protocol. BAW, RW, and GMG were responsible for modelling and analyses; BAW, RW and EH drafted the manuscript; and BAW, PA, PAA, EH, RW, and GMG provided input to discussions. All authors have read and approved the final version of the manuscript.

Data sharing statement

Study data are available from the corresponding author on reasonable request

Figure legends

Figure 1 Reasons for immigration for immigrants aged < 35 years arriving in Norway in 2008-2011, by country of origin (%).

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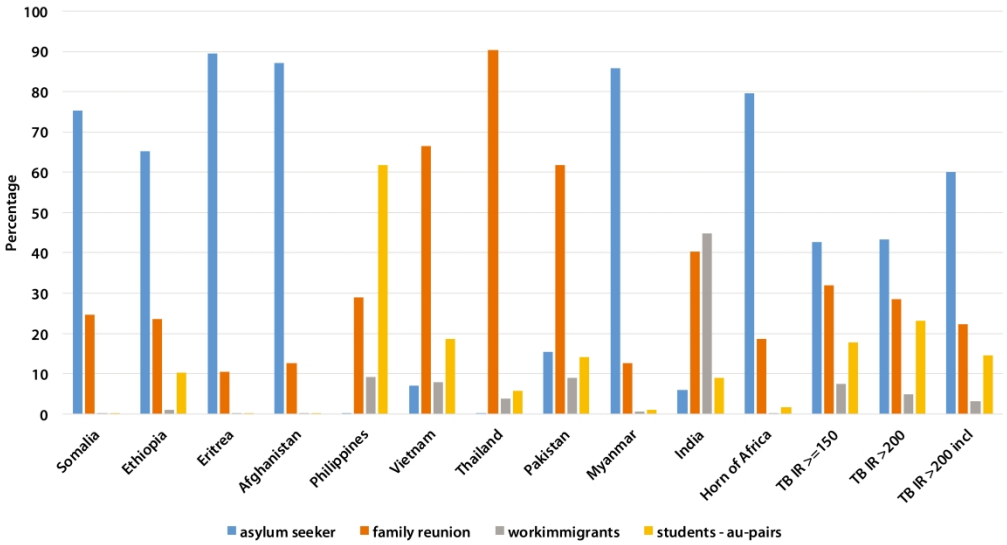

Figure 1 Reasons for immigration for immigrants aged < 35 years arriving in Norway in 2008-2011, by country of origin (%).

Appendices 1a-d and 2

Appendix 1a, Data sources and information provided

Source	Information provided
IMMIGRATION AND EMIGRATION DATA	
Norwegian Directorate of Immigration (UDI) (aggregated data)	**Immigration**: Total number of asylum seekers applying for residence in Norway by country of citizenship and by year of application (2008-2014). Age-distribution was reported as proportions by country of citizenship **Emigration**: Data on the number of immigrants who later emigrated. Time before emigration were based on the number of days from date of application to date of final rejection of application by country of citizenship and by year. Data were obtained as percentiles, i.e. the number of days reported as the 10th percentile reflected the number of days from date of application until date of final rejection for the ten percent with the shortest observation time, and so on.
Statistics Norway (SSB) (aggregated data)	**Immigration**: Total number of given residence permits for students, work immigrants, au-pairs and family reunifications in Norway by country of birth and year (2008-2014). Age-distribution was reported by country of birth and reason for immigration (proportions) **Emigration**: Information on average time in Norway before emigration by reason for immigration and year. Estimates are based on data from 2014.
CASE DATA	
Norwegian Surveillance System for Infectious diseases (MSIS) (case-based data)	Persons notified with TB or preventive treatment of latent TB in Norway, 2008 – 2016: individual-level data including category (TB or LTBI preventive treatment), age, country of birth, date of notification, date of diagnosis (collection of clinical sample), date of start of treatment and time in Norway prior to date of diagnosis (categorized as <1 month, 1-6 months, 7-12 months, 1-2 years, 3-4 years, 5-9 years, and >10 years)

Appendix 1b, Definitions

Definitions	Estimates
Immigration and emigration	We defined an immigrant as a person who applied for asylum or who received a residence permit (other immigrant groups). We defined emigration as having received a final rejection of application for asylum or being recorded as emigrated in SSB.
Country of origin	This reflects citizenship for asylum seekers and country of birth for other immigrant groups.
Number immigrants arriving in 2008-2011 and who eligible for screening	We estimated the proportion aged <15 years and 15-35 years by country, reason for immigration and year of immigration based on the reported age-distribution from SSB/UDI. Refugees: 83% < 35 yrs. Among them 18% are 0-14 yrs and 82% 15-34 yrs Family-reunification: 80% < 35 yrs, among them 44% are 0-14 yrs and 56% are 15-34 yrs. Work immigrants: 70%, among them all are 15-34 yrs. Students and au-pairs: 95%, among them all are 15-34 yrs

LTBI	Latent tuberculosis infection. We used positive IGRA as a proxy for LTBI.
Number of LTBI	The prevalence of LTBI in the immigrant cohort was estimated by multiplying the number of arriving immigrants with the published estimates of IGRA positives, based on published literature, including a Norwegian publication. Estimates of IGRA positivity ranged from 18%-29%, depending on estimated TB incidence rate in country of origin and age-group; 0-14 yrs and 15-35yrs.
TB and LTBI treatment	We used the categorical information about time in Norway prior to diagnosis from MSIS to estimate a probability distribution for each case's arrival year in Norway. We then estimated the number of individuals with TB or LTBI treatment who belonged to the 2008-2011 cohort of immigrants by multiplying the number of cases by the probability that they immigrated to Norway in 2008-2011.
Preventable TB	We defined preventable TB as a TB patient notified to MSIS with TB and who: (i) arrived to Norway in 2008-2011, (ii) was notified to MSIS > 1 month (6 months) and < 5 years after arrival, (iii) was younger than 40 years of age at notification (to allow for five years observation time after screening). We excluded TB cases that were on TB treatment on arrival to Norway. We then used this number and adjusted for QFT sensitivity 84% (81% -87%), treatment effectiveness at 65% (50%-80), and treatment completion rates at 90% (80% - 100%) to estimate the final number of preventable TB cases belonging to the 2008-2011 cohort.

Appendix 1c, Model assumptions

That immigrants who received residence permit or applied for asylum actually immigrated to Norway. That immigrants that later were registered as emigrated, or had a final rejection of application for asylum, actually emigrated.
That all immigrants eligible for screening were screened and that they were screened soon after arrival in line with regulations.
That the age- and country specific prevalence of LTBI from published literature, including Norwegian data, is a fair proxy for the prevalence in the arrival cohort.
That a person did not leave Norway after receiving LTBI treatment.

Appendix d, Indexes

Index	Calculation	The use of the indexes
Duration of time spent in Norway (cumulative probability distribution)	Table Y1	To estimate the number of people remaining in Norway in year X who arrived in year Y
Estimated people remaining in Norway in year X who arrived in year Y	Number of arriving immigrants in year Y * proportion of immigrants who remain in Norway for at least (X-Y) years	To calculate person years under observation for the cohort
Person years under observation for the cohort	Estimated number of years spent in Norway for immigrants who arrived in years 2008-2011	Used as the exposure time for the cohort
Risk of preventable TB per time-period	For each time period after arrival to Norway (<1 month, 1-6 months, 7-12 months, 1-2 years, 3-4 years, 5-9 years, and >10 years) we obtained the	Used to calculate the additional preventable TB (see description below)

	number of preventable TB cases and then calculated the risk of preventable TB per time period (i.e. number of cases divided by number of people).	
Monthly risk of preventable TB within time-period	1-(1-risk)^(1/numbermonths).	Used to calculate the 5 year risk of preventable TB without emigration
Number needed to screen (NNS)	Number of arriving immigrants/number of preventable TB	Primary outcome
Crude number needed to treat (NNT)	Number of LTBI positive immigrants/number of preventable TB (a combined effect of emigration and TB risk)	Primary outcome for immigrants without taking emigration into account.
Corrected number needed to treat (NNT)	1/risk of preventable TB (TB risk corrected for the effect of emigration)	NNT measure that is independent of emigration
Number of TB prevented by LTBI treatment	Number of LTBI treated*risk of preventable TB in the different time periods based on the first five years in Norway. Calculations for time periods were based on LTBI positive individuals who remained at risk 1-6 months, 7-12 months, 13-36 months and 37-60 months after arrival to Norway.	Secondary outcome to estimate the number of TB prevented in Norway from the screening programme
Additional preventable TB	We calculated the percentage increase in prevented TB (potential for additional prevention) when LTBI treatment was initiated within the first (i) 6 months and (ii) 12 months after arrival to Norway (based on the 84% sensitivity/65% treatment effectiveness/90% adherence estimates and incident TB > 1 month after arrival).	Secondary outcome to estimate the effect of delay of LTBI treatment initiation

Appendix 2. Number of notified TB cases from the top ten source countries for immigrant TB in Norway, 2008-2015 (Source: MSIS*)

Countries	2008	2009	2010	2011	2012	2013	2014	2015	Total
Somalia	70	106	72	106	112	102	84	47	699
Eritrea	12	24	16	20	23	41	47	49	232
Philippines	20	14	25	23	30	25	26	25	188
Pakistan	20	18	23	20	15	18	15	8	137
Ethiopia	9	27	17	14	15	16	17	15	130
Afghanistan	7	10	19	16	11	18	11	26	118
Thailand	10	16	15	10	11	8	14	13	97
Vietnam	10	15	12	11	7	15	12	7	89
India	7	9	7	4	11	12	9	6	65
Myanmar	11	6	10	8	7	7	3	2	54

MSIS, Norwegian Surveillance System for Infectious Diseases

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract, page 1 title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found, page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported, page 4
Objectives	3	State specific objectives, including any prespecified hypotheses, page 4
Methods		
Study design	4	Present key elements of study design early in the paper page 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection , page 4 and 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up page 4 and 5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable page 5-8, appendices 1a-d
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group page 4 and 5, appendix 1a
Bias	9	Describe any efforts to address potential sources of bias, page 6 and 7
Study size	10	Explain how the study size was arrived at page 5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why page 5-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding page 5-7
		(*b*) Describe any methods used to examine subgroups and interactions page 5-7
		(*c*) Explain how missing data were addressed page 6
		(*d*) If applicable, explain how loss to follow-up was addressed page 6
		(*e*) Describe any sensitivity analyses page 6 and 7
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed page 6 and 7
		(b) Give reasons for non-participation at each stage page 6
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders table 2, page 10
		(b) Indicate number of participants with missing data for each variable of interest, na (model)
		(c) Summarise follow-up time (eg, average and total amount) table 2, page 10
Outcome data	15*	Report numbers of outcome events or summary measures over time table3 and 4, page 11 and 12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included table 3, page 11
		(*b*) Report category boundaries when continuous variables were categorized na
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses table 4, page 12
Discussion		
Key results	18	Summarise key results with reference to study objectives page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias page 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence page 15 and 16
Generalisability	21	Discuss the generalisability (external validity) of the study results page 16
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based page 16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Immigrant screening for latent tuberculosis infection – numbers needed to test and treat: A Norwegian population-based cohort study

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Immigrant screening for latent tuberculosis infection – numbers needed to test and treat: A Norwegian population-based cohort study

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ABSTRACT

Objectives Estimate the numbers needed to screen (NNS) and treat (NNT) to prevent one tuberculosis (TB) case in the Norwegian immigrant LTBI screening programme, and to explore the effect of delay of LTBI treatment initiation.

Design Population-based prospective cohort study

Participants Immigrants to Norway

Outcome Incident TB

Methods We obtained aggregated data on immigration to Norway in 2008-2011 and used data from the Norwegian Surveillance System for Infectious Diseases to assess the number of TB cases arising in this cohort within 5 years after arrival. We calculated average NNSs and NNTs for immigrants from the top 10 source countries for TB in Norway and by estimated TB incidence rates (IRs) in source countries. We explored the sensitivity of these estimates regarding test performance, treatment efficacy, and treatment adherence using an extreme value approach, and assessed the effects of emigration, time to TB diagnosis (to define incident TB), and intervention timing.

Results
NNSs and NNTs were overall high, with substantial variation. The NNT showed numerically stronger negative correlation with the TB notification rate in Norway [-0.75 (95% CI 1.00 to -0.44)] than with the World Health Organisation IR [-0.32 (95% CI -0.93 to 0.29)]. NNTs were affected substantially by emigration and the definition of incident TB. Estimates were lowest for Somali [NNS 99 (70-150), NNT 27 (19-41)] and highest for Thai immigrants [NNS 585 (413-887), NNT 117 (83-178)]. Implementing LTBI treatment in immigrants sooner after arrival may improve the effectiveness of the programme.

Conclusions
Using TB notifications in Norway, rather than IR in source countries, would improve targeting of immigrants for LTBI management. However, the overall high NNT is a concern and challenges the scale-up of preventive LTBI treatment for significant public-health impact. Better data are urgently needed to monitor and evaluate NNS and NNT in countries implementing LTBI screening.

Strengths and limitations of this study

- A population-based and sensitive surveillance system provided national data on all new cases of tuberculosis
- Country-specific administrative data were used to estimate person-time under observation for immigrants
- We applied different estimates of latent TB test sensitivity, treatment efficacy and adherence to treatment to calculate uncertainty
- The prevalence of latent tuberculosis infection in recent immigrants was estimated from published surveys rather than individual data
- Some cases of tuberculosis present upon arrival may have been misclassified as having onset after arrival

BACKGROUND

The World Health Organisation (WHO) have issued guidelines for the programmatic management of latent tuberculosis infection (LTBI).[1 2] The guidelines strongly recommend screening for and treatment of LTBI in groups at high-risk for tuberculosis (TB) and conditionally in recent immigrants from high- to low TB incidence countries.[1] LTBI is common and the risk of progression to TB varies substantially among individuals, assumed to reflect age, time since infection, and host immune status.[1]

The identification of target immigrant groups for LTBI management remains challenging in most low-TB incidence settings. There has been a call for the harmonisation of migrant screening policies across Europe.[3] Eligibility for screening is commonly based on the TB IR in the country of origin or the reason for immigration, with typical focus on asylum seekers and refugees.[3] It has, however, been suggested that the targeting of immigrants based on the TB IR in the host country may improve the effectiveness of immigrant screening programmes.[4]

In Norway, foreign-born individuals account for almost 90% of TB notifications and the majority are diagnosed in the first 5 years after arrival.[5] Based on molecular surveillance of *Mycobacterium tuberculosis* strains, the majority of TB in the foreign-born population is assumed to reflect reactivation of LTBI acquired prior to arrival.[5] Against this backdrop, Norway has a well-established immigrant screening programme for TB and LTBI. Immigrants are currently targeted for TB screening based on the WHO-estimated TB incidence rates (IRs) in their countries of birth.[6] Immigrants younger than 35 years are also targeted for LTBI management to prevent future development of TB. The eligibility for arrival LTBI screening has differed over time; in March 2017 the IR cut-off value was changed from >40/100,000 to >200/100,000 (including immigrants from Afghanistan and Eritrea).[7] The monitoring and evaluation system of the long-standing TB and LTBI screening programme is weak.

The primary objective of this study was to use aggregated numbers of Norwegian immigration and individual level TB surveillance data to estimate the of number needed to screen (NNS) and number needed to treat (NNT) with LTBI chemoprophylaxis to prevent one TB case in the immigrant LTBI screening programme. Secondary objectives were to estimate the number of TB cases prevented by the current strategy in a 4-year cohort of immigrants, and to explore the effect of delay of LTBI treatment initiation within the first 6 months versus the 12 months after arrival, using the same immigration and surveillance data.

METHODS

Data sources and creation of data set for modelling and analysis

We combined aggregate numbers from Norwegian immigration data (i.e. information on the entire cohort) and individual level TB surveillance data (i.e. information on individuals with TB or LTBI treatment) to create a unified dataset for modelling and analysis. All steps are described in the text below. A complete overview is also presented in table format in appendices 1a-d.

Data and sources

Immigration and emigration data

We have used administrative data on immigration by year, country of origin, and reason for immigration in Norway in 2008-2011. Data were obtained separately from two different sources: the Norwegian Directorate of Immigration (UDI) for newly arrived asylum seekers and from Statistics Norway (SSB) for other immigrant groups. The number of immigrants is based on number of asylum applications and number of residence permits for other immigrant groups. Country of origin reflects

citizenship for asylum seekers and country of birth for other immigrant groups. We estimated the proportion aged <15 years and 15-35 years by country, reason for immigration and year of immigration based on the reported age-distribution from SSB/UDI (appendix 1a). As emigration from Norway is substantial in some immigrant groups, we obtained aggregated administrative data on time spent in Norway before emigration from the same sources (further described below). In the model, we have assumed that immigrants who received residence permit or applied for asylum actually immigrated to Norway and that immigrants who were later registered as emigrated, or had a final rejection of application for asylum, actually emigrated (appendix 1c).

TB cases and LTBI treatment

For individuals with TB and LTBI treatment (i.e. the people of interest), individual-level demographic and clinical information was obtained from the Norwegian Surveillance System for Infectious Diseases (MSIS) for the years 2008-2016. This time-period allows for five years observation time for all immigrants. The information included age at notification, country of birth, date of notification, date of diagnosis (collection of clinical sample) and date of start of treatment. Further, on the MSIS notification form, clinicians report time in Norway prior to diagnosis for foreign-born individuals using the following categories: <1 month, 1-6 months, 7-12 months, 1-2 years, 3-4 years, 5-9 years, and >10 years. Date of arrival is not reported.

It is mandatory for laboratories and clinicians to report TB diagnosis and treatment outcome, and prescription of LTBI treatment, to MSIS. Untreated LTBI is not reported. The sensitivity of MSIS data is assumed to be high because notifications are sent from multiple sources and are checked routinely against TB drug prescriptions.

We used all TB notifications to MSIS in 2008-2015 (year of reporting) to identify the top 10 source countries (in absolute numbers; appendix 2) for immigrant TB in Norway and then calculated the TB notification rate (NR) in Norway based on the number of observation years.

Construction of analysis dataset

Based on the aggregated immigration data we calculated the number of arriving immigrants aged ≤ 35 years from the top 10 source countries for TB in Norway and for countries with WHO-estimated TB IRs > 150/100,000 population in the period 2008-2011. We used the WHO Global TB Report 2014 estimates of TB IR in countries of origin in 2013.[6]

Estimated prevalence of LTBI

We used a positive IGRA as a proxy for LTBI. The prevalence of IGRA positives was based on published literature, including Norwegian data on asylum seekers,[8] and ranged from 18% to 29%, depending on the WHO-estimated TB IR in the country of origin and the age group; 0-14 years and 15-35 years.[8-10] The number of immigrants with LTBI in the model was estimated by multiplying the number of arriving immigrants with the published estimates of IGRA positives, separately for the two age-groups. In the model we have assumed that the age- and country specific prevalence of LTBI from published literature, including Norwegian data, is a fair proxy for the LTBI prevalence in the arrival cohort.

TB and LTBI treatments in the 2008-2011 immigrant cohort

We used the categorical information about time in Norway prior to diagnosis from MSIS to estimate a probability distribution for each case's arrival year in Norway (e.g. "a case received a diagnosis in December 2010 and has been in Norway for <1 month, therefore they have 100% probability that they arrived in Norway in 2010 and belong to the 2008-2011 immigrant cohort", "a case received a diagnosis in March 2012 and has been in Norway for 1-6 months, therefore they have a 50%

probability that they arrived in Norway in 2011, and 50% probability that they arrived in Norway in 2012"). When information about time since arrival was missing, we imputed this information by applying the country-specific probability distribution for time-in-Norway. We then estimated the number of individuals with TB or LTBI treatment who belonged to the 2008-2011 cohort of immigrants by multiplying the number of cases by the probability that they immigrated to Norway in 2008-2011.

We excluded individuals who were diagnosed with TB (based on the date of sample collection for TB diagnosis) within 1 month after arrival, as these individuals were most likely ill on arrival (co-prevalent TB) and TB would not be preventable through LTBI screening and treatment. For sensitivity analysis, we also excluded individuals who were notified within 1-6 months. These cases may or may not have been preventable through LTBI management. Based on this uncertainty, we present NNSs and NNTs separately for TB diagnosed >1 and >6 months after arrival, and applied these two definitions of incident TB throughout the study.

Estimation of time in Norway

Since emigration is substantial in some immigrant groups, we estimated the cumulative probability of time under observation in Norway based on UDI/SSB administrative data. For asylum seekers, data on emigration was obtained as percentile distributions of number of days from application date to date of final rejection of application, e.g. among 421 asylum seekers from Somalia who arrived in Norway in 2008 and whose application for asylum later was rejected, 10% were rejected within 62 days, 20% were rejected within 87 days and so on up until the 90% percentile. We used this information to calculate the number of person-years of observation lost due to emigration within the first five years after arrival in Norway. This was done separately by country, TB IR in country of citizenship and by year.

For other immigrant groups, data on emigration was based on aggregated September 2014 data, containing the number of immigrants per year and the number of them that emigrated before September 2014 (separately by reason for immigration). See Table 1 for an example of the data and the formulae used to estimate the cumulative probability distribution for duration of time in Norway for the cohort.

Table 1. The cumulative probability distribution for duration of time in Norway for immigrants other than asylum seekers.

Year of arrival (X)	Number arrived in year X	Number emigrated before 09/2014	Average time in Norway as of 09/2014	cumulative proportion staying in Norway as of 09/2014
2008	D1	N1	6,25	1-N1/D1
2009	D2	N2	5,25	1-N2/D2
2010	D3	N3	4,25	1-N3/D3
2011	D4	N4	3,25	1-N4/D4

Finalizing dataset

Using the prior pieces of information (number of people arriving each year, probability distribution of time to emigration, and for each TB/LTBI diagnosis – time since immigration and estimated year of arrival) we created a dataset containing yearly cohorts of people who immigrated to Norway between 2008 and 2011 and are followed up for either five years or until they emigrate from Norway (the shorter of the two).

Outcomes

Preventable TB/Risk of preventable TB

We defined preventable TB as a patient notified with TB to MSIS and who: (i) arrived to Norway in 2008-2011, (ii) was notified to MSIS > 1 month (6 months) and < 5 years after arrival, (iii) was younger than 40 years of age at notification (to allow for five years observation time after screening). With this relatively short time period, we assume that they were infected prior to arrival in Norway. We explored the sensitivity of these estimates regarding test performance, treatment efficacy and adherence to treatment using an extreme value approach. IGRA sensitivity was estimated to be 84% (with 81% and 87% applied as extreme values)[11 12] and chemoprophylaxis efficacy was estimated to be 65% (50%-80%),[1 13] consistent with a UK study.[4] The rate of treatment adherence was estimated to be 90% (80%-100%), based on previous studies, including Norwegian data.[14-17] The number of incident TB cases was adjusted accordingly and defined as preventable TB (table 2). We excluded TB cases that were on TB treatment on arrival to Norway.

For each time period after arrival to Norway (<1 month, 1-6 months, 7-12 months, 1-2 years, 3-4 years, 5-9 years, and >10 years) we obtained the number of preventable TB cases and then calculated the risk of preventable TB per time period (i.e. number of cases divided by number of people). The risk of developing TB during this time period was then also converted into monthly risk using the formula 1-(1-totalrisk)^(1/number-months).

NNS and NNT

We estimated the NNS to prevent one incident TB case by calculating the ratio of the number of arriving immigrants to the number of preventable TB cases observed in Norway within 5 years. We used the extreme value approach to explore the sensitivity of these estimates.

We estimated the *crude NNT* as the ratio of the number of individuals testing positive for LTBI to the number of preventable TB cases. This NNT can be interpreted as a combined effect of emigration and TB risk (i.e. if someone emigrates from Norway they cannot receive a TB diagnosis in Norway, thus the more emigration the lower the risk for TB observed in Norway). We used the information on person years lost for observation due to emigration to calculate *corrected NNT* as 1/(risk of preventable TB in 5 years). This number can be interpreted as the NNT if all immigrants remained in Norway for 5 years.

We then explored correlation with 95% confidence intervals (CIs) of the NNT with the TB NR in Norway and WHO-estimated TB IR. The purpose of this analysis was to identify which data source (TB NR in Norway or WHO-estimated TB IR) had a stronger association with public health implications in Norway (NNT).

Prevented TB due to LTBI treatment and the effect delay of LTBI treatment initiation

We estimated the expected number of TB prevented by the LTBI treatments provided during the study period. This was calculated by multiplying the number of LTBI treatments by the subsequent risk of preventable TB in different time-periods (based on the categorical MSIS data on time since arrival). The calculations were limited to the first 5 years in Norway (e.g. if a person received LTBI treatment after 4 years in Norway, LTBI treatment would have a preventive effect for only 1 year). In the model, we have assumed that all immigrants eligible for screening actually were screened and that they were screened soon after arrival in line with the mandatory screening programme. We further assumed that a person did not leave Norway after receiving LTBI treatment. Calculations were based on incident TB > 1 month after arrival.

We calculated the percentage increase in prevented TB (potential for additional prevention) when LTBI treatment was initiated within the first (i) 6 months and (ii) 12 months after arrival to Norway (based on the 84% sensitivity/65% treatment effectiveness/90% adherence estimates and

incident TB > 1 month after arrival) through multiplying increased number of people screened by sensitivity by effectiveness by adherence. The outcome reflects a combination of the timing of TB diagnosis and LTBI treatment, or a strong effect of one of them.

Uncertainty in the calculations

None of the calculations in this study included uncertainty. Our model was primarily deterministic. The source of uncertainty in our study came from running our deterministic model with alternative IGRA sensitivities and treatment efficacies (the extreme value approach).

Patient and Public Involvement

Patients and or the public were not involved in the study

RESULTS

The majority of foreign-born TB patients in Norway originated from the Horn of Africa; Somalia alone accounted for 44% of TB cases from the top 10 source countries (table 2). Overall, a high proportion of TB occurred within the first year after arrival, with some variation among source countries. The fraction of observation years lost due to emigration was substantial in some groups and varied among source countries (table 2).

Most immigrants from the Horn of Africa, Afghanistan, and Myanmar arrived as refugees and asylum seekers (figure 1). Most immigrants from Vietnam, Thailand, and Pakistan arrived for family reunification, whereas immigrants from India arrived for family reunification and work, and the majority of immigrants from the Philippines came to work as au-pairs.

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Overall, estimated NNSs and NNTs were high (table 3). Estimates were lowest for Somalia: screening of 70-150 and treatment of 19-41 Somali immigrants was required to prevent one incident TB case (6 months threshold for preventable TB). NNTs were lowest for estimates corrected for the effect of emigration and with the 1-month threshold to define incident TB, compared to the crude NNT and the 6 months threshold (table 3). The same pattern was seen for all countries. NNTs were highest for immigrants from Pakistan and Thailand, although NNSs were substantially higher for Thailand. For most source countries, the number of preventable TB cases was reduced by one-third when the 6-month definition of incident TB was applied compared with the 1-month definition, but with variation (range 16%-75%).

We found a stronger numerical correlation between the TB NR in Norway and NNT to prevent one incident TB case [correlation coefficient (CC) -0.75 (95% CI -1.00 to -0.44)] than between the NNT and WHO-estimated IR in the country of origin [CC -0.32 (95% CI -0.93 to 0.29)] for the top 10 source countries for TB in Norway (using corrected NNTs and the 6-month definition of incident TB). The CCs were affected only modestly by emigration and definition of incident TB, and unaffected by the extreme value approach (data not shown). The WHO-estimated TB IRs in Somalia and Pakistan in 2013 were similar (274 and 270/100,000 person-years). These values contrast with our findings that NNTs were lowest for Somali immigrants and among the highest for Pakistani immigrants. The WHO-estimated TB IR in the Philippines is high, and the NNSs and NNTs were high in our setting. NNTs for immigrants from Pakistan and Thailand were similar, although the estimated TB IR is substantially lower in Thailand than in Pakistan. When eligibility for screening was based on TB IRs in countries of origin, NNTs were fairly similar for the different thresholds and highest for those with IRs

> 200/100,000, including Eritrea and Afghanistan. Estimates were lowest for immigrants from the Horn of Africa.

Only a small percentage (range 3% - 21%) of LTBI-positive immigrants were estimated to have received LTBI treatment (table 4). The resulting estimated number of incident TB cases prevented by LTBI treatment was therefore modest, with a limited overall public-health impact of the immigrant LTBI screening programme in Norway in this period.

Almost half (range 30%-58%) of LTBI treatments were prescribed >12 months after arrival in Norway (table 4). The highest percentages were for immigrants from the Horn of Africa, where most incident TB occurs. A substantial proportion of additional incident TB cases could have been prevented if the same number of LTBI treatments had been prescribed sooner after arrival (table 4).

Table 2 TB and LTBI among immigrants aged < 35 years arriving in Norway in 2008-2011 by country of origin. (Only top ten source countries for TB in Norway listed by country).

Country of origin (WHO estimated annual TB incidence rate per 100,000)[a]	Arrivals in Norway in 2008-2011[b] (<35 years)	Estimated no. of LTBI cases[c]	Notified TB in Norway first 5 years after arrival (<40 years)		Time in Norway prior to TB diagnosis (months)				TB within 12 months after arrival	Person-years under observation[d]	Observation years lost due to emigration[e]
					< 1	1–6	7–12	13–60			
	(n)	(n)	(n)	NR	(n)	(n)	(n)	(n)	(%)	(n)	(proportion)
By country											
Myanmar (369)	900	255	18	419	1	7	4	6	67	4300	0.06
Philippines (288)	6700	1909	64	358	1	29	14	20	69	17,900	0.47
Somalia (274)	7400	2019	252	900	23	74	54	101	60	28,000	0.25
Pakistan (270)	2000	520	12	174	0	3	2	7	42	6900	0.29
Ethiopia (207)	2400	651	46	667	5	8	9	24	48	6900	0.42
Afghanistan (189)	6800	1417	44	238	4	10	7	23	48	18,500	0.46
Thailand (171)	3900	776	20	120	1	6	2	11	45	16,600	0.14
India (167)	2800	682	18	167	1	3	2	12	28	10,800	0.23
Vietnam (140)	900	177	12	364	0	9	1	2	83	3300	0.25
Eritrea (78)	6900	1888	82	307	10	21	15	36	56	26,700	0.22
Horn of Africa[f]	*16,700*	*4558*	*380*	*679*	*38*	*103*	*78*	*161*	*58*	*61,700*	*0.26*
Countries grouped by estimated TB incidence rate[a]											
>150/100,000	37,100	7058	533	446	43	161	104	225	58	119,400	0.36
>200/100,000	23,300	5485	428	595	35	137	87	169	61	72,000	0.38
>200/100,000 incl[g]	37,000	8692	554	473	49	167	110	228	59	117,200	0.37

TB, tuberculosis; NR, notification rate per 100,000 person years under observation; LTBI, latent tuberculosis infection.

[a] From the 2014 World Health Organisation Global tuberculosis control report. [6]

[b] Number of immigrants, rounded to the nearest hundred. Data were obtained from Statistics Norway and the Norwegian Directorate of Immigration.

[c] Interferon-gamma release assay positivity was used as a proxy for LTBI (estimates are based on published data, including Norwegian data).

[d] Adjusted according to estimated time in Norway before emigration for immigrants arriving in Norway in 2008-2011.

[e] Estimated proportion observation years lost due to emigration within the first 5 years after arrival

[f] Including Somalia, Eritrea, and Ethiopia.

[g] Includes countries with TB IRs > 200/100,000 and Eritrea and Afghanistan (in line with current Norwegian guidelines)

Table 3 Estimated numbers of preventable TB cases and the numbers of immigrants needed to screen (NNS) and to treat (NNT) for latent tuberculosis infection to prevent one case of tuberculosis in the first five years after arrival, among immigrants arriving in Norway 2008-2011.

Country of origin (WHO estimated TB incidence rate per 100,000)[a]	Incident TB based on diagnosis ≥ 1 month after arrival				Incident TB based on diagnosis > 6 months after arrival			
	Preventable TB[b,c]	NNS[c,d]	NNT, crude[c,e]	NNT, corrected[c,f]	Preventable TB[b,c]	NNS[c,d]	NNT, crude[c,e]	NNT, corrected[c,f]
By country								
Myanmar (369)	8 (12–6)	111 (78–168)	30 (22–46)	na*	5 (7–3)	181 (128–274)	50 (35–76)	*na
Philippines (288)	31 (44–20)	218 (154–330)	62 (44–94)	59 (42–89)	16 (23–11)	419 (296–635)	119 (84–180)	104 (74–158)
Somalia (274)	113 (159–74)	66 (47–100)	18 (13–27)	13 (10–20)	75 (107–50)	99 (70–150)	27 (19–41)	17 (12–26)
Pakistan (270)	6 (9–4)	319 (225–484)	85 (60–129)	75 (53–113)	4 (6–3)	440 (311–668)	117 (83–178)	94(67–143)
Ethiopia (207)	20 (29–13)	118 (83–179)	32 (23–49)	23 (16–34)	16 (22–10)	152 (108–231)	42 (29–63)	26 (19–40)
Afghanistan (189)	20 (28–13)	347 (245–526)	72 (51–109)	46 (32–69)	15 (22–10)	444 (313–673)	92 (65–140)	54 (38–82)
Thailand (171)	9 (13–6)	414 (292–628)	83 (59–126)	78 (55–119)	7 (9–4)	585 (413–887)	117 (83–178)	111 (79–169)
India (167)	8 (12–6)	334 (236–506)	82 (58–124)	75 (53–113)	7 (10–5)	396 (279–600)	97 (68–147)	89 (63–135)
Vietnam (140)	6 (8–4)	151 (107–229)	30 (21–46)	28 (20–42)	1 (2–1)	605 (427–917)	120 (85–182)	93 (66–141)
Eritrea (78)	35 (50–23)	194 (137–295)	53 (38–81)	43 (31–65)	24 (34–16)	286 (202–433)	78 (55–119)	56 (40–85)
Horn of Africa[g]	*168 (238–111)*	*99 (70–151)*	*27 (19–41)*	*15 (11–23)*	*115 (163–76)*	*145 (103–220)*	*40 (28–60)*	*18 (13–27)*
Countries grouped by estimated TB incidence rate [a]								
>150/100,000	241 (341–159)	154 (109–234)	32 (23–49)	23 (16–35)	160 (226–105)	232 (164–352)	48 (34–73)	30 (21–45)
>200/100,000	193 (274–127)	121 (85–183)	28 (20–43)	20 (15–31)	124 (175–82)	188 (133–286)	44 (31–67)	27 (19–41)
>200/100,00 incl[h]	248 (351–164)	149 (105–226)	35 (25–53)	23 (16–34)	163 (231–108)	227 (160–344)	53 (38–81)	29 (20–43)

Estimates include TB occurring after 1 and 6 months and within the first 5 years following arrival in Norway, 2008-2011.

TB, tuberculosis; NNS and NNT, numbers needed to screen and treat to prevent one incident TB case within the first 5 years after arrival.

*Emigration is minimal (na) since the majority arrived as refugees under the United Nations High Commissioner for Refugees and were granted residency prior to arrival

[a] From the 2014 World Health Organisation Global tuberculosis control report. [6]

[b] Number of TB patients notified from screening cohorts, adjusted regarding diagnostic test sensitivity, treatment efficacy, and adherence.

[c] Using the point estimate with (range) of sensitivity, efficacy, and adherence estimates.

[d] Ratio of the number of new arrivals to the number of preventable TB cases observed in Norway.

[e] Ratio of the number of latent tuberculosis infection and preventable TB cases observed in Norway, i.e. combined effect of emigration and risk of TB.

[f] 1 / risk of preventable TB for a person who stayed in Norway for 5 years, i.e. corrected for the effect of emigration.

[g] Including Somalia, Eritrea, and Ethiopia.

[h] Includes countries with TB IRs > 200/100,000 and Eritrea and Afghanistan (in line with current Norwegian guidelines).

Table 4 Estimated numbers of tuberculosis cases prevented by latent tuberculosis infection treatment of immigrants during the first 5 years after arrival in Norway, 2008-2011.

Country of origin (WHO estimated TB incidence rate per 100,000)[a]	TB notification (<40 years)	LTBI treatment (<40 years)[b]	Time of LTBI treatment after arrival (months)			LTBI treatment > 12 m after arrival	Number of incident TB cases prevented by LTBI treatment (range)[c]	Additional preventable incident TB cases if all LTBI treatments were initiated within 6 or 12 months after arrival	
			≤6	7-12	13-60				
	(n)	(n, %)	(n)	(n)	(n)	(%)	(n)	6 months (%)	12 months (%)
By country									
Myanmar (369)	18	54 (21)	23	15	16	30	3 (4–2)	21	9
Phil4ppines (288)	64	200 (10)	61	68	71	35	2 (3–1)	57	11
Somalia (274)	252	391 (19)	64	113	215	55	19 (27–13)	38	15
Pakistan (270)	12	16 (3)	4	4	9	52	0.2 (0.2–0.1)	22	7
Ethiopia (207)	46	108 (17)	13	37	58	54	3 (5–2)	15	8
Afghanistan (189)	44	159 (11)	32	54	74	46	3 (4–2)	18	7
Thailand (171)	20	53 (7)	13	15	25	47	0.5 (0.7–0.3)	30	4
India (167)	18	21 (3)	6	8	7	33	0.2 (0.3–0.2)	10	2
Vietnam (140)	12	26 (15)	8	10	8	32	0.5 (0.6–0.3)	99	4
Eritrea (78)	82	195 (10)	21	60	113	58	3 (6–2)	42	16
Horn of Africa[d]	*380*	*694 (15)*	*98*	*210*	*386*	*56*	*32 (45–21)*	*25*	*12*
Countries grouped by estimated TB incidence rate [a]									
>150/100,000	533	1193 (17)	267	381	545	46	36 (51–24)	30	10
>200/100,000	428	900 (16)	198	288	414	46	30 (42–20)	34	12
>200/100,000 incl[e]	554	1252 (14)	250	402	600	48	39 (55–26)	29	11

TB, tuberculosis; LTBI, latent tuberculosis infection

[a] From the 2014 World Health Organisation Global tuberculosis control report.[6]

[b] Percentage of LTBI positive persons with LTBI treatment.

[c] Highest and lowest estimates using the point estimate with (range) of sensitivity, efficacy, and adherence estimates.

[d] Including Somalia, Eritrea, and Ethiopia.

[e] Includes countries with TB IRs > 200/100,000 and Eritrea and Afghanistan (in line with current Norwegian guidelines).

DISCUSSION

The NNS and NNT to prevent one adverse outcome are measures used to communicate the effectiveness of health care interventions.[18] In this study of the immigrant LTBI screening programme in Norway, we found overall very high NNSs and NNTs to prevent one incident TB case, and higher than in previous studies.[4 19] Screening based on the TB NR in Norway rather than the TB IRs in source countries improved targeting of immigrants for LTBI management. However, NNSs and NNTs remained high for most countries by either approach, even when we applied the most optimistic estimates for test sensitivity, treatment effectiveness, and treatment adherence.

Strengths and limitations

The strengths of this study include the availability of detailed country-specific administrative immigration and emigration data that provides a strong estimate of the person-time observation for recent immigrants, the high sensitivity of the TB and LTBI surveillance system, and the performance of comprehensive sensitivity analyses for the different estimates. Given the availability of information on time in Norway prior to TB diagnosis or LTBI treatment from MSIS, we were able to demonstrate the effect of intervention timing. This approach has important clinical implications. Lastly, the overall consistency with the UK study[4] makes comparison possible.

Study limitations include the currently weak monitoring and evaluation system of the Norwegian LTBI screening programme. Multiple service providers are involved in the screening process, with no harmonisation of data collection or follow-up documentation. Substantial delays in the provision of government-issued personal ID numbers to recent immigrants, specifically asylum seekers, have compromised follow-up and data linkage. For the same reason, we could not calculate NNTs based on absolute risk reduction in LTBI-treated individuals. The lack of denominator data is a common challenge in most countries, which renders immigrant screening programmes poorly evaluated. We have used comprehensive administrative data and high-coverage surveillance data including information on LTBI treatment, to overcome these limitations.

Screening coverage is high among asylum seekers and refugees, but less known for other immigrant groups (family reunification, students and immigrant workers). If screening participation was non-selective, it would not affect our estimates. However, if the prevalence of LTBI differed among those screened and not screened, our estimates may be biased.

The prevalence of LTBI in the arriving immigrant cohort was based on published literature, including Norwegian data on asylum seekers. [8-10] Whether these correctly reflects the prevalence of LTBI in the arriving cohort is unknown and this may potentially have biased our estimates in either direction. If the LTBI prevalence in the arriving immigrants was lower than estimated, the reported NNSs and NNTs would be too high, whereas with a higher prevalence than estimated our NNSs and NNTs would be too low.

Norwegian guidelines encourage treatment of individuals at greatest risk of progression to TB. If LTBI-positive individuals prescribed LTBI treatment were at greater risk than untreated LTBI-positive individuals, we may have underestimated the number of TB cases prevented by LTBI treatment during the study period. We may also have underestimated the overall benefit of the screening programme, as incident TB occurring >5 years after arrival was not included. However, whether incident TB occurring several years after arrival is related to initial infection or subsequent re-infection is difficult to evaluate in long-term follow-up studies. A Dutch study of molecular data in contacts showed that 83% of incident cases occurred within 5 years of the source case and >95% occurred within 10 years,[20] suggesting that the degree of potential underestimation was modest. Finally, the effects of screening for TB and LTBI are difficult to disentangle, as they contribute to each other.

Comparison with other studies

A UK study documented substantial variation in NNSs and NNTs among immigrants from the 10 most commonly reported source countries for TB in the UK.[4] The figures contrasted with estimated TB IRs in the source countries. Similarly, we found great variation in NNSs and NNTs, which were not consistently related to estimated WHO TB IRs in source countries. Immigrants may originate from specific geographical areas with higher or lower rates than national averages, and their socio-economic circumstances before and after arrival in host countries may differ. Surprisingly, the estimated NNTs for source countries were overall considerably higher in Norway than in the UK. NNTs for immigrants from Pakistan were 85 (60-129) and 34 (17-70), from Somalia 18 (13-27) and 4 (1-7) and from India 82 (58-124) and 37 (20-61) in Norway and UK respectively.[4] In the current study, we differentiated between co-prevalent and incident TB and accounted for emigration; both factors have profound impacts on NNTs and were not assessed in the UK study.[4] Immigrants are screened soon after arrival in Norway, and many leave the country before the end of the 5-year observation period. In contrast, the UK study examined long-term immigrants. Differences in TB epidemiology may also contribute to the observed differences. The UK researchers reported higher TB rates, and therefore also higher transmission rates, than in most Western European countries, specifically in larger cities.[21] The higher estimates for treatment adherence in this study compared with the UK study would narrow, rather than widen, the difference in NNTs. A mathematical modelling study from Australia found that a combination of screening and subsequent treatment of all LTBI positive immigrants would result in an overall reduction in number of TB cases of about one-third to one-half from 2013 - 2050.[19] The NNSs were 297 for all immigrants and 136 for immigrants originating from countries with an estimated TB IR >100/100 000, which is somewhat lower than in the current study. As in the UK study the model was based on permanent arrivals.

Challenges of NNS/NNT estimation in immigrant screening

The lifetime age-weighted risk of TB following infection in settings with low exogenous re-infection is estimated to be 12%.[22] The reported low pooled positive predictive value of the IGRA (2.7%) corresponds to an NNT of 37 across different settings and populations.[23] This corresponds to 111 months of treatment to prevent one TB case in need of 6 months of treatment. Thus, the risk reduction following LTBI treatment must be large to reduce the NNT. Although morbidity, mortality, and transmission can be avoided if TB is prevented, the benefit of LTBI treatment for the individual should outweigh the risk of severe adverse effects. Although LTBI treatment is safe overall, it carries a risk of severe and potentially life-threatening toxic adverse effects.[24]

Register data did not allow us to clearly distinguish co-prevalent TB from TB that developed later and was potentially preventable through LTBI management (incident TB). LTBI is considered to comprise a spectrum of infection states.[25] A prolonged asymptomatic phase of early subclinical TB may precede clinical presentation with active disease.[26 27] A pre- and post-arrival evaluation of a cohort of US immigrants reported that >80% of TB cases diagnosed within 1 year of receiving pre-arrival examination represented co-prevalent TB.[27] TB diagnosed <1 month after arrival is clearly not preventable, whereas TB diagnosis within 1-6 months may or may not be preventable. Based on this uncertainty, we presented NNSs and NNTs separately for TB diagnosed >1 and >6 months after arrival.

Emigration was substantial in some groups. Immigrants to Norway from Myanmar were almost exclusively refugees under the United Nations High Commissioner for Refugees and were granted residency prior to arrival, whereas applications from adult asylum seekers from Afghanistan commonly were rejected. The observation years lost due to emigration were also substantial in other groups with high proportions of asylum seekers. Immigrants from the Philippines often arrive as au-

pairs and are granted only 2-year work permits. Emigration may also lead to NNT overestimation if immigrants who show LTBI positivity on screening upon arrival in Norway develop TB after emigration.

The effect of timeliness of screening and treatment

In this study, less than one in five estimated LTBI-positive individuals (if all immigrants were screened) was treated. This gap in the *intention to screen is intention to treat* principle represents a challenge and has been reported in other Norwegian studies;[28-30] it has been due partly to Norwegian guidelines (in which the groups targeted for screening has been wider than those targeted for treatment), and measures have been taken to minimise it.[7] It may, however, also signal that the number of LTBI-positive individuals is too high for the health services to treat, and/or that clinicians are reluctant to initiate LTBI treatment in individuals with unknown risk of progression to disease.

As a high proportion of incident TB cases occur early after arrival, an important component to improve the impact of the screening programme would be to ensure expedited follow-up and LTBI treatment initiation. Increased attention is given to the need for timely interventions as the incubation period for TB.[31] The reduced risk of progression to TB over time will increase NNT estimates with time, and delayed follow-up represents missed opportunities. The potential for additional prevented cases varied across countries of origin. The high potential for additional prevention among immigrants from Vietnam reflects the high proportions of those who are ill early after arrival and those for whom LTBI treatment is initiated late, whereas the opposite was observed for India.

Comparing NNT to TB NR in Norway and WHO estimated IRs in countries of origin

We found a stronger numerical correlation between the NNT and TB NR in Norway than between the NNT and WHO-estimated IR in the country of origin for the top 10 source countries for TB in Norway. This is expected, as both the NRs and the NNT estimates are derived from the same Norwegian data (representing the same subset of the population who immigrated to Norway, which may not be a representative sample of the people in the country of origin), whereas the WHO-estimated IRs use country-specific data to make representative estimates for their national populations. When a large difference exists between the people in the country of origin and the subset of the population who immigrated to Norway, we would expect the TB NR in Norway to be more programmatically useful than the WHO estimated IRs in countries of origin.

Public health implications

The overall high NNSs and NNTs in this study call into question whether routine LTBI screening of immigrants in a high-income low-incidence country is feasible, safe and effective, without the application of additional selection criteria. Although LTBI management based on TB notification in Norway rather than WHO estimated IRs in countries of origin, would have improved the targeting of immigrants, the NNSs and NNTs remained high.

The estimated number of incident TB cases prevented by LTBI treatment was modest suggesting that substantial scale-up of the LTBI care cascade is necessary to strengthen the public health impact. Until new tests with higher predictive values for TB are available,[25] there are two complementary approaches to reduce the NNSs and NNTs. Firstly, screening could be limited to immigrants with additional risk factors for disease, such as young age, recent known contact, abnormal x-ray findings, and immunosuppressive conditions. This approach, however, will require additional resources to correctly identify risk groups on entry. Secondly, the LTBI care cascade could be improved so that further examinations and treatment are offered sooner following a positive LTBI screening test. The programme has the potential to prevent additional TB cases if more immigrants

with LTBI are offered treatment, and this treatment starts sooner after arrival. TB disease develops usually 3-9 months after exposure and rarely more than two years after exposure,[31] which strengthens the recommendation for prompt follow-up of immigrant screening. A combination of these two approaches seems most plausible. Cost-effectiveness studies could help to identify the most beneficial approach in a Norwegian setting.

Monitoring of the effectiveness of screening should urgently be improved, by targeting immigrants with risk factors in addition to the TB IR in the source country and ensuring timely follow-up of screening. The data in Norway are better than in many other countries, but still with wide uncertainty. As immigration trends and composition and health services vary considerably among countries, better monitoring and evaluation of current screening programmes are needed so that countries can adjust their policies based on the yield of screening.

Even when applying the most optimistic estimates regarding diagnostic test sensitivity, treatment efficacy, and adherence to treatment, a substantial proportion of incident TB cases will not be prevented through LTBI screening and management. Easy and equitable access to health care services for all should remain a cornerstone of tuberculosis control and prevention so that clinical cases are detected and treated early.

Ethical approval

Ethical approval of the study was obtained from Regional Committee for Medical and Health Research Ethics, south east Norway (2017/164).

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Competing interests statement

None declared.

Authors' contributions

BAW initiated the study, and BAW and EH wrote the protocol. BAW, RW, and GMG were responsible for modelling and analyses; BAW, RW and EH drafted the manuscript; and BAW, PA, PAA, EH, RW, and GMG provided input to discussions. All authors have read and approved the final version of the manuscript.

Data sharing statement

Study data are available from the corresponding author on reasonable request

Figure legends

Figure 1 Reasons for immigration for immigrants aged < 35 years arriving in Norway in 2008-2011, by country of origin (%).

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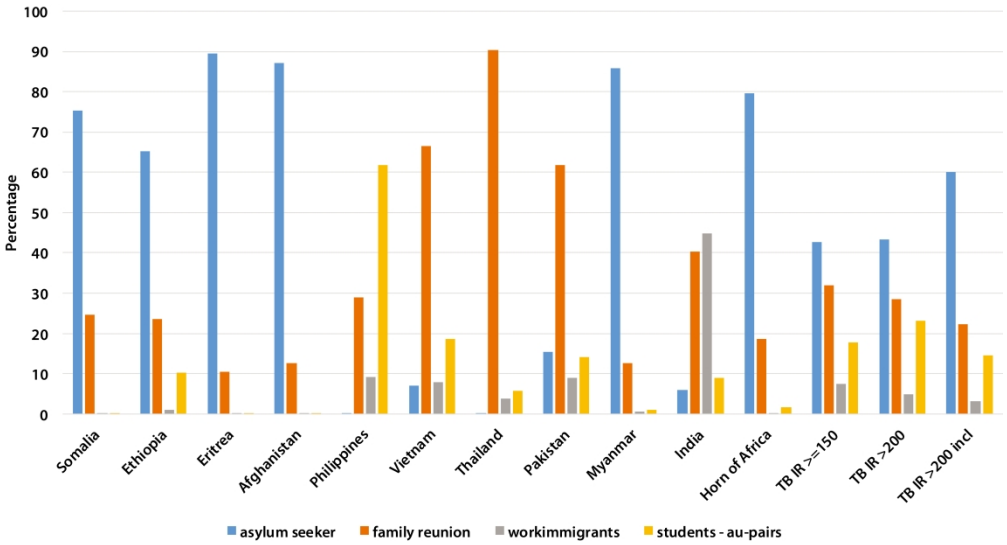

Figure 1 Reasons for immigration for immigrants aged < 35 years arriving in Norway in 2008-2011, by country of origin (%).

Appendices 1a-d and 2

Appendix 1a, Data sources and information provided

Source	Information provided
IMMIGRATION AND EMIGRATION DATA	
Norwegian Directorate of Immigration (UDI) (aggregated data)	**Immigration**: Total number of asylum seekers applying for residence in Norway by country of citizenship and by year of application (2008-2014). Age-distribution was reported as proportions by country of citizenship **Emigration**: Data on the number of immigrants who later emigrated. Time before emigration were based on the number of days from date of application to date of final rejection of application by country of citizenship and by year. Data were obtained as percentiles, i.e. the number of days reported as the 10th percentile reflected the number of days from date of application until date of final rejection for the ten percent with the shortest observation time, and so on.
Statistics Norway (SSB) (aggregated data)	**Immigration**: Total number of given residence permits for students, work immigrants, au-pairs and family reunifications in Norway by country of birth and year (2008-2014). Age-distribution was reported by country of birth and reason for immigration (proportions) **Emigration**: Information on average time in Norway before emigration by reason for immigration and year. Estimates are based on data from 2014.
CASE DATA	
Norwegian Surveillance System for Infectious diseases (MSIS) (case-based data)	Persons notified with TB or preventive treatment of latent TB in Norway, 2008 – 2016: individual-level data including category (TB or LTBI preventive treatment), age, country of birth, date of notification, date of diagnosis (collection of clinical sample), date of start of treatment and time in Norway prior to date of diagnosis (categorized as <1 month, 1-6 months, 7-12 months, 1-2 years, 3-4 years, 5-9 years, and >10 years)

Appendix 1b, Definitions

Definitions	Estimates
Immigration and emigration	We defined an immigrant as a person who applied for asylum or who received a residence permit (other immigrant groups). We defined emigration as having received a final rejection of application for asylum or being recorded as emigrated in SSB.
Country of origin	This reflects citizenship for asylum seekers and country of birth for other immigrant groups.
Number immigrants arriving in 2008-2011 and who eligible for screening	We estimated the proportion aged <15 years and 15-35 years by country, reason for immigration and year of immigration based on the reported age-distribution from SSB/UDI. Refugees: 83% < 35 yrs. Among them 18% are 0-14 yrs and 82% 15-34 yrs Family-reunification: 80% < 35 yrs, among them 44% are 0-14 yrs and 56% are 15-34 yrs. Work immigrants: 70%, among them all are 15-34 yrs. Students and au-pairs: 95%, among them all are 15-34 yrs

LTBI	Latent tuberculosis infection. We used positive IGRA as a proxy for LTBI.
Number of LTBI	The prevalence of LTBI in the immigrant cohort was estimated by multiplying the number of arriving immigrants with the published estimates of IGRA positives, based on published literature, including a Norwegian publication. Estimates of IGRA positivity ranged from 18%-29%, depending on estimated TB incidence rate in country of origin and age-group; 0-14 yrs and 15-35yrs.
TB and LTBI treatment	We used the categorical information about time in Norway prior to diagnosis from MSIS to estimate a probability distribution for each case's arrival year in Norway. We then estimated the number of individuals with TB or LTBI treatment who belonged to the 2008-2011 cohort of immigrants by multiplying the number of cases by the probability that they immigrated to Norway in 2008-2011.
Preventable TB	We defined preventable TB as a TB patient notified to MSIS with TB and who: (i) arrived to Norway in 2008-2011, (ii) was notified to MSIS > 1 month (6 months) and < 5 years after arrival, (iii) was younger than 40 years of age at notification (to allow for five years observation time after screening). We excluded TB cases that were on TB treatment on arrival to Norway. We then used this number and adjusted for QFT sensitivity 84% (81% -87%), treatment effectiveness at 65% (50%-80), and treatment completion rates at 90% (80% - 100%) to estimate the final number of preventable TB cases belonging to the 2008-2011 cohort.

Appendix 1c, Model assumptions

That immigrants who received residence permit or applied for asylum actually immigrated to Norway. That immigrants that later were registered as emigrated, or had a final rejection of application for asylum, actually emigrated.
That all immigrants eligible for screening were screened and that they were screened soon after arrival in line with regulations.
That the age- and country specific prevalence of LTBI from published literature, including Norwegian data, is a fair proxy for the prevalence in the arrival cohort.
That a person did not leave Norway after receiving LTBI treatment.

Appendix d, Indexes

Index	Calculation	The use of the indexes
Duration of time spent in Norway (cumulative probability distribution)	Table Y1	To estimate the number of people remaining in Norway in year X who arrived in year Y
Estimated people remaining in Norway in year X who arrived in year Y	Number of arriving immigrants in year Y * proportion of immigrants who remain in Norway for at least (X-Y) years	To calculate person years under observation for the cohort
Person years under observation for the cohort	Estimated number of years spent in Norway for immigrants who arrived in years 2008-2011	Used as the exposure time for the cohort
Risk of preventable TB per time-period	For each time period after arrival to Norway (<1 month, 1-6 months, 7-12 months, 1-2 years, 3-4 years, 5-9 years, and >10 years) we obtained the	Used to calculate the additional preventable TB (see description below)

	number of preventable TB cases and then calculated the risk of preventable TB per time period (i.e. number of cases divided by number of people).	
Monthly risk of preventable TB within time-period	1-(1-risk)^(1/numbermonths).	Used to calculate the 5 year risk of preventable TB without emigration
Number needed to screen (NNS)	Number of arriving immigrants/number of preventable TB	Primary outcome
Crude number needed to treat (NNT)	Number of LTBI positive immigrants/number of preventable TB (a combined effect of emigration and TB risk)	Primary outcome for immigrants without taking emigration into account.
Corrected number needed to treat (NNT)	1/risk of preventable TB (TB risk corrected for the effect of emigration)	NNT measure that is independent of emigration
Number of TB prevented by LTBI treatment	Number of LTBI treated*risk of preventable TB in the different time periods based on the first five years in Norway. Calculations for time periods were based on LTBI positive individuals who remained at risk 1-6 months, 7-12 months, 13-36 months and 37-60 months after arrival to Norway.	Secondary outcome to estimate the number of TB prevented in Norway from the screening programme
Additional preventable TB	We calculated the percentage increase in prevented TB (potential for additional prevention) when LTBI treatment was initiated within the first (i) 6 months and (ii) 12 months after arrival to Norway (based on the 84% sensitivity/65% treatment effectiveness/90% adherence estimates and incident TB > 1 month after arrival).	Secondary outcome to estimate the effect of delay of LTBI treatment initiation

Appendix 2. Number of notified TB cases from the top ten source countries for immigrant TB in Norway, 2008-2015 (Source: MSIS*)

Countries	2008	2009	2010	2011	2012	2013	2014	2015	Total
Somalia	70	106	72	106	112	102	84	47	699
Eritrea	12	24	16	20	23	41	47	49	232
Philippines	20	14	25	23	30	25	26	25	188
Pakistan	20	18	23	20	15	18	15	8	137
Ethiopia	9	27	17	14	15	16	17	15	130
Afghanistan	7	10	19	16	11	18	11	26	118
Thailand	10	16	15	10	11	8	14	13	97
Vietnam	10	15	12	11	7	15	12	7	89
India	7	9	7	4	11	12	9	6	65
Myanmar	11	6	10	8	7	7	3	2	54

MSIS, Norwegian Surveillance System for Infectious Diseases

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract, page 1 title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found, page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported, page 4
Objectives	3	State specific objectives, including any prespecified hypotheses, page 4
Methods		
Study design	4	Present key elements of study design early in the paper page 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection , page 4 and 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up page 4 and 5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable page 5-8, appendices 1a-d
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group page 4 and 5, appendix 1a
Bias	9	Describe any efforts to address potential sources of bias, page 6 and 7
Study size	10	Explain how the study size was arrived at page 5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why page 5-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding page 5-7
		(*b*) Describe any methods used to examine subgroups and interactions page 5-7
		(*c*) Explain how missing data were addressed page 6
		(*d*) If applicable, explain how loss to follow-up was addressed page 6
		(*e*) Describe any sensitivity analyses page 6 and 7
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed page 6 and 7
		(b) Give reasons for non-participation at each stage page 6
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders table 2, page 10
		(b) Indicate number of participants with missing data for each variable of interest, na (model)
		(c) Summarise follow-up time (eg, average and total amount) table 2, page 10
Outcome data	15*	Report numbers of outcome events or summary measures over time table3 and 4, page 11 and 12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included table 3, page 11
		(*b*) Report category boundaries when continuous variables were categorized na
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses table 4, page 12
Discussion		
Key results	18	Summarise key results with reference to study objectives page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias page 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence page 15 and 16
Generalisability	21	Discuss the generalisability (external validity) of the study results page 16
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based page 16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.