Evaluating the effectiveness of interventions for the prevention of tuberculosis in a low-incidence setting
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Chapter 7 General Discussion
The aim of this thesis was to determine the effectiveness of specific TB control interventions and methods, taking a broad definition of effectiveness to include the size of the problem, the coverage and yield of the intervention and resource requirements. All studies were performed to monitor and evaluate the performance and the impact of the interventions, and the results were used as evidence to adjust the intervention or target the intervention to specific risk groups. The discussion is organized into sub-sections according to the specific questions. For each study, the research findings are summarized and recommendations and implications for the policy are elaborated upon. Where applicable, further policy developments and further research questions are described at the end of each subsection.

**Entry and follow-up screening for TB in immigrants**

In this study we showed that in the period 1998-2002 the yield of entry screening was above the threshold set in the Netherlands for risk group screening: a TB incidence of 50 per 100,000. The effectiveness of the entry screening was high to the extent that more than 90% of the prevalent cases were detected through screening. Remarkably, the yield of the entry screening among the two largest immigrant population groups, immigrants from Morocco and Turkey (152 and 91 per 100,000, respectively), was higher than the prevalence in the country of origin estimated by WHO (86 and 44 per 100,000, respectively). The effectiveness of the follow-up screening in terms of coverage, yield and proportion of the incident TB cases detected through the screening was less favorable. Overall coverage of follow-up screening was low and declined further with every round of screening. The yield of follow-up screening was low among persons from countries with a WHO-estimated TB incidence of less than 200 per 100,000. Abnormalities in the chest X-ray at entry were the most important predictor for development of TB, irrespective of the incidence in the country of origin. The findings in our study were consistent with another study in the Netherlands(1) which showed that incidence remained high many years after immigration. A cost-effectiveness study of the screening of immigrants using the data from the Monitoring of Screening of Immigrants (MSI) project (2) showed that the cost-effectiveness of radiological screening of immigrants, and of the follow-up screening in particular was unfavorable, as was also observed in other studies(3, 4). However, several studies found that LTBI screening among new immigrants was cost-effective when combined with preventive treatment(5).

Based on the evidence from the MSI report, the CPT decided in 2007 to target the follow-up screening of immigrants and asylum seekers to those from areas with a WHO-estimated TB incidence of 200 per 100,000 or more. Since this change in policy, the coverage and yield of the TB screening among immigrants has been evaluated in 2009 and 2012 with data of immigrant cohorts entering the Netherlands in 2003-2004 and 2005-2010(6). The main conclusions of these reports were:

1. The yield of the entry screening among immigrants from low-endemic areas (WHO estimation <50 per 100,000) had decreased in the period 2005-2010 to well below the criterion of 50 per 100,000;

2. TB incidence among immigrants from high endemic countries (incidence at least 200 per 100,000) during the first two years after entry in the periods 2003-2004 and 2005-2010 was 193 and 146 per 100,000 person years follow-up respectively;
the coverage of the follow-up screening decreased from on average 59% in the 1st follow-up screening in the period 1998-2002 to on average 47% in the period 2005-2010.

Following the recommendation in the last report the CPT advised the Ministry of Health to consider exempting immigrants from countries with a WHO-estimated TB incidence rate below 50 per 100,000 from the mandatory TB screening (unless observed prevalence rates from the screening yield are well over 50 per 100,000) and adjust the Immigration Act accordingly. The changes in the Immigration Act came into effect as of January 1st, 2015. The Immigration Act requires reference to a list endorsed by the CPT with the annually updated WHO estimates of TB incidence(7, 8). Through these policy adjustments the annual number of immigrants eligible for TB screening decreased with an estimated 27%(6). Moreover, replacing the follow-up screening by LTBI screening and preventive treatment is proposed as a main strategy to the reduce the burden of TB in the Netherlands in 2020 with 25%(9). LTBI screening will be introduced step-wise starting with high-priority groups such as children and immigrants from high endemic countries. The implementation of this approach will be monitored closely through a research project supported by ZonMW (TB-Endpoint), and cost-effectiveness and impact of LTBI screening will be evaluated to guide policy decisions on extending the intervention to other risk groups.

Added value of interferon gamma release assays for LTBI diagnosis in the Netherlands

The study on the added value of IGRA for LTBI diagnosis aimed to prospectively determine the impact of this novel diagnostic test for LTBI in terms of numbers of persons identified with LTBI and eligible for preventive treatment and to estimate the incremental costs of screening algorithms with IGRA compared to the conventional algorithm with TST only. The study showed that when using TST in combination with IGRA as a confirmatory test, the IGRA changed the diagnostic result for 41% of the individuals with a TST of 5 mm and more, with an incremental cost per LTBI patient diagnosed of €124, and with 86% of the expected incremental cost compensated for by a reduction in the costs required for preventive treatment. Based on this evidence and these cost-effectiveness considerations, the CPT guidelines now recommend a 2 step algorithm with TST followed by IGRA if the reaction size is 5 mm or more, taking the IGRA result as the final outcome (i.e. confirmatory). However, other studies have shown that in specific settings the use of IGRA alone may be more cost-effective(10), specifically when used in an immigrant population.

The ability to predict the risk of progression to TB disease is imperfect for both the TST and the IGRA and it is recommended to choose the diagnostic tests for LTBI on the basis of specificity in specific populations, logistics, cost, and patients’ preferences(11). It is not clear to what extent the Dutch policy to base LTBI diagnosis on IGRA results leads to under-treatment of persons at risk of developing TB, as cohorts included in our study were not actively followed up to determine TB incidence. However, it is possible to address this limitation through matching the cohort data with the NTR. Through this method of passive follow-up the number of persons in the study cohort developing TB and reported to the national TB surveillance system within 2 years after testing can be determined and risk factors for progression to active TB can be analyzed further.
Since 2010, the likelihood of infection among those targeted for LTBI screening may have increased as the guidelines for contact investigation, screening of health care workers, other professionals at risk and travelers have been revised, and LTBI screening in these groups is more targeted to those with a higher likelihood of recent exposure. The National Plan for TB control 2016-2020 advocates to screen immigrants and asylum seekers for LTBI. Among new immigrants, Mulder et al. reported a prevalence of TST positivity of 13-24% (12), but LTBI prevalence data for asylum seekers are not available. Furthermore, the cost of the IGRA has decreased since 2011 and the cost of TST increased. So it is likely that the cost-effectiveness of the recommended screening algorithm in immigrants and asylum seekers differs from that of the traditional target groups for LTBI screening in the Netherlands. The question which groups of immigrants and asylum seekers can best be targeted for LTBI screening and which test algorithms for LTBI are preferable from the health service as well as from the clients’ perspective is currently being addressed in the research project ‘TB-Endpoint’ supported by ZonMW.

**Room for prevention of childhood TB**

The assessment of TB control efforts among children in the Netherlands showed that the quality of diagnosis and case management is high compared with that in other low burden countries, and early case finding and prevention of TB in children is ensured through systematic contact investigation of infectious TB patients and preventive treatment of children with LTBI. Still we found that TB rates in foreign-born and second-generation immigrant children did not decline proportionally to rates among adults from those population groups. We concluded that in more than one in three children with TB the disease could potentially have been prevented, particularly through improved implementation of the BCG-vaccination policy for children of high risk groups and through LTBI screening and preventive treatment of migrant children upon entry in the Netherlands. According to a recent review the effectiveness of BCG-vaccination in low endemic areas could be as high as 80% for all forms of TB, not only for serious disseminated forms of TB (13). Based on a cost-effectiveness analysis using notification data from the NTR (14) the National Health Council in 2011 advised to continue the targeted BCG-vaccination policy and improve the coverage of BCG-vaccination in children aged of 6 months and above with a parent originating from countries with a WHO estimated incidence of 50 per 100,000 population or more (15).

In our study we looked at missed opportunities for TB prevention through BCG-vaccination in the present target group for BCG. Our estimate of the number of cases that could have been prevented is uncertain, because coverage of BCG-vaccination is uncertain. The Health Council estimated a coverage of 60% (15). Other childhood disease vaccinations performed through the National Immunization Program reach an overall coverage of 95%. Improvement of the coverage of BCG-vaccination could be achieved by making use of the National Immunization Program structures.

But apart from improving the coverage of BCG-vaccination in the target group, more cases among newborn children could possibly be prevented if the age of vaccination would be lowered to immediately after birth, as recommended by WHO. In 2016 the guideline for BCG-vaccination of children from high-risk populations will be revised. The CPT is taking the latter option into consideration, and has committed to increasing the coverage and timeliness of BCG vaccination (9).
Another important opportunity for prevention of childhood TB in the Netherlands is LTBI screening and preventive treatment of child immigrants and asylum seekers on entry in the Netherlands replacing the screening for active TB. In December 2015 the CPT already endorsed this policy for children aged younger than 18 years. The effectiveness of this approach needs to be closely monitored and evaluated.

Effectiveness of LTBI management

Trends in LTBI diagnosis and management
Addressing the pool of persons infected with M. tuberculosis through preventive treatment is regarded as one of the pillars to achieve TB elimination in 2050(16). The Netherlands has been performing and monitoring LTBI management since 1993 and is typically regarded to be at the forefront in TB control and prevention(17). The Dutch data offered a unique opportunity to report on the experience with LTBI management, using the indicators recommended for the evaluation in the guideline(17). In addition we discussed the strengths and limitations of programmatic LTBI management and estimated the impact on TB epidemiology. The study showed that over a period of more than 20 years 37,729 persons newly diagnosed with LTBI were notified to the NTR, of whom 28,931 (77%) were started on preventive treatment. Of those initiating preventive treatment 82% completed, 6% interrupted treatment due to adverse events, and 12% interrupted for other causes or were lost to follow-up. Children younger than 15 years of age, contacts of infectious TB patients and persons with (expected iatrogenic) immunosuppression were more likely to start preventive treatment. These groups were also more likely to complete preventive treatment, as were professionals at risk of exposure to TB, travelers and persons receiving a shorter regimen. The occurrence of adverse events was associated with increasing age, female gender, Dutch origin, rural residence, (expected iatrogenic) immunosuppression and isoniazid monotherapy. Remarkably, although initiation and completion of treatment were associated negatively with increasing age and the occurrence of adverse events increased with age, even in the age groups 35 years and older treatment completion was still well above 80%, and preventive treatment was relatively well tolerated with the occurrence of serious adverse events varying between 10-14%. The results are generally more favorable than what has been reported in studies from other low incidence settings(18, 19). Despite the relatively favorable operational outcomes of the Dutch LTBI program, we estimated that with the present tools, and based on the rates of preventive treatment initiation and completion, an overall 40-60% of incident TB was prevented in the study population. To achieve elimination safer, shorter and more effective possibilities for preventive treatment are desperately needed.

Impact of LTBI diagnosis and preventive treatment
In the study described in Chapter 6 we found that up to March 1, 2014, the cumulative TB incidence was 0.6% among the population notified to the NTR in the period 2005-2013 who completed preventive treatment, and 1.8% and 1.3% respectively among those who interrupted or did not receive preventive treatment. The overall rate was lower than expected on the basis of studies of the lifetime risk of tuberculosis after infection(20, 21). After controlling for age, likelihood of TB exposure and immune status, completing preventive treatment reduced the risk of developing TB compared to not receiving preventive treatment. The risk reduction was not significant among
target groups other than TB contacts. The overall risk reduction (59-68%) was slightly lower than the reduction observed in RCTs of 60-90% (17). In Chapter 5 we estimated the overall impact of preventive treatment among the population based on the RCTs between 40% and 60%. Using the more setting-specific data for The Netherlands reported in Chapter 6 for this estimate, the overall impact of preventive treatment among the population identified with LTBI calculated in Chapter 5 is more likely to be around 40%. Moreover, the effect was only visible in the first and the second year after LTBI diagnosis. Therefore, based on these results, we recommend to prioritize LTBI screening to populations with a high risk of having been recently infected, such as TB contacts and children younger than 5 years, and to immunocompromised persons with a high risk of progression to TB as is recommended by WHO (17).

This means that LTBI screening practices in other target groups need to be critically reviewed. In recent years the Dutch guidelines for TB prevention in groups generally perceived as having a higher risk of TB exposure than the general population such as health care workers, professionals in contact with TB risk groups and travelers to endemic areas, have already been revised by the CPT. For all these groups, the CPT recommends LTBI screening only for those with a real risk of exposure: in the context of contact investigation or as evidenced by 'high' levels of incident TB in the local epidemiological situation. However, PMHSs perform the screening of professional groups in lieu of occupational health services, who often let employer liability and employee security concerns prevail over (cost-)effectiveness. In daily practice more persons are screened for LTBI than the professional guidelines recommend as evidenced by the comparatively large group of LTBI notifications in the target group category ‘pre-exposure’. Our study provides the evidence to convince employers and institutions to rationalize their practices according to the recommendations of the CPT guidelines.

On the other hand, offering LTBI screening and preventive treatment to immigrant populations with a high risk to develop TB could have more impact on TB epidemiology, and may contribute considerably to the goal of TB elimination (12). But the risk to develop TB is variable in migrant groups and new migrants may not be familiar to the concept of TB prevention through preventive treatment. Therefore LTBI screening of migrants raises new operational questions: what subgroups among the migrant population should be targeted to achieve optimal impact on TB epidemiology and what is the right approach to achieve high acceptance of the screening and preventive treatment in these groups. The research project TB Endpoint will address these issues, through pilot projects targeting migrant groups known to have the highest risk to develop TB for LTBI screening and evaluate the effectiveness through a combination of qualitative, quantitative and modelling studies. The results will be used to write a business case for LTBI screening, that should guide policy makers in the final decision making process to in the choice of target groups and LTBI screening algorithms.

**Strengths and limitations of current TB and LTBI surveillance data**

The strength of the Netherlands TB register is that it was designed not only as a disease surveillance system (22), but also as a tool to provide professionals insights into the contribution of risk factors to the burden of TB, to support policy evaluation and to provide information for fundamental and operational research in the field of TB control. Similarly, registration of persons diagnosed with LTBI
provides insight into the effectiveness of TB prevention through screening and treatment of LTBI. The data are used by epidemiologists, policymakers and researchers, and reported to the general public on a regular basis. The content of the data collection is annually updated and adjusted to the current demands of TB control.

The studies in Chapter 4, 5 and 6 made use of the routinely collected TB surveillance and notification data in the Netherlands TB register on TB patients and persons notified with LTBI. Based on a capture-recapture study, we are confident that the TB data are very complete and representative for the TB situation in the Netherlands(23). We are also confident the data for LTBI cases diagnosed by the TB control sector are complete, since they are regularly checked against client registry data of the PMHSs. However, important target groups for LTBI testing and treatment such as persons diagnosed with HIV and persons eligible for treatment with TNF-alfa inhibitors are more often tested in the clinical sector and we do not know what proportion of LTBI cases diagnosed in the clinical sector is captured in the database. A study describing the occurrence of TB among persons receiving TNF-alfa inhibitors in the Netherlands found that from 2005 to 2011 the total number of persons on treatment with TNF-alfa inhibitors increased from approximately 13,600 in 2005 to 36,520 in 2011. On average this amounts to at least 4000 new individuals annually at increased risk for progression to TB when latently infected(24). Based on an average background prevalence of LTBI in the Netherlands of 2%, one would expect at least 80 persons per year identified with LTBI in this group. However, the number could be higher depending on the average age of those eligible for treatment with TNF-alfa inhibitors, because the background prevalence of LTBI increases with age.

The number of persons with LTBI notified to the NTR and found through screening in the context of immune suppression increased from 31 in 2005 to 167 in 2014(25) which suggests in the latter years more clinical LTBI cases have been captured. Annually approximately 1100 new persons are diagnosed with HIV-infection in the Netherlands(26). The policy in the Netherlands is to screen for LTBI all persons with newly detected HIV infection who have risk factors for TB infection(27). However, the LTBI register does not distinguish between different causes of immune suppression (HIV-infection, use of TNF-alfa inhibitors or other immune suppressive treatment) and we have no insight in the proportion of those eligible for LTBI screening for clinical reasons that is actually screened. To assess the effectiveness of TB prevention in this particular group, more details are needed on the reason of immune suppression and quality of the diagnosis. Therefore, the data collection form needs to be adjusted and clinicians need to be motivated to report persons newly diagnosed with LTBI to the PMHSs, like they do for TB patients.

A concern related to any surveillance system is the quality of the data recorded. The study populations for the study in Chapter 2 (evaluating the screening policy) and in Chapter 3 (evaluating the LTBI diagnostic algorithm) were cohort data on eligible persons screened, collected from the different client registries of PMHSs. This was a laborious process leading to possible data entry mistakes. Since the central electronic client register ‘TUBIS’ came in place in 2010, it became possible to retrieve demographic data and screening results through a single download. Standardization of the client register improved the quality of the study data considerably and the mandatory use of the social security number decreased the chance of duplicate records. As for the quality of the NTR, the staff of the TB department in the MPHS enter the data manually into the
Osiris web system using information from the patient record. Where possible, automated checks on accuracy are built in the web system and a check on consistency and completeness of key data is systematically done by the data managers from RIVM for each record. Still, the quality of the data is directly influenced by the quality of the patient record, how well the TB staff is informed about the ins and outs of the NTR questionnaire and if the data are double checked for accuracy and completeness.

Very little is known about the quality of TB surveillance registers in different countries. The WHO Global Task Force on TB Impact Management has developed a checklist and user guide to strengthen TB surveillance and assist countries with self-assessment of the TB surveillance data (28). A CPT subcommittee charged with the evaluation and review of the NTR applied the WHO checklist and concluded that in some PMHSs internal auditing and supervision of timeliness, accuracy and completeness of the data is lacking and training of staff recording the data could be further improved, although overall completeness of the data is acceptable. Ultimately, for both the client register TUBIS and the NTR, the quality of the data recorded in the client register remains a continuous concern. Regular feedback can sensitize staff to the importance of accurate, consistent and complete recording of the data used for M&E and surveillance. Despite these concerns, less than 5% records were excluded in the studies for incomplete or inaccurate data so we consider the quality of the Dutch TB surveillance data to be satisfactory and the conclusions of the Dutch surveillance data our studies to be valid.

An important indicator of the effectiveness of screening is the coverage of the intervention among the target group. The studies in Chapter 2 and Chapter 5 evaluating the effectiveness of immigrant entry screening and LTBI screening did not include the coverage because of the difficulty to obtain exact data on the size of the target groups. PMHSs do not have direct information on the number of immigrants eligible for entry screening and information on the number of persons annually eligible for LTBI screening is not collected on national level. In Chapter 2 we did assess the coverage of the follow-up screening among immigrants screened on entry. The coverage we found was likely to be underestimated as the PMHSs had no information on the number of immigrants who left the country during the follow-up period. It was shown in a study in 1996 that the percentage of immigrants who left the country within one year after entry screening amounted to 26% (29). When corrected for immigrants leaving the cohort, the coverage increased from 58 to 68% in the first follow-up screening.

Aggregated information on the size of the population may be available from population statistics or other public institutions serving the target population for TB interventions. When available in sufficient detail to distinguish the specific target group such data can help to make an estimate of the coverage, but a precise calculation can only be made with case-based records of the population targeted for intervention linked to the intervention data with unique identifiers. To make this feasible privacy concerns and practical impediments related to (electronic) databases would need to be addressed.

In the studies in Chapter 2 and Chapter 6 we calculated rates of incident TB based on the number of TB cases notified to the NTR which matched the cases in the cohort of new immigrants screened on
entry c.q. the cohort of cases notified with LTBI. As a consequence of this method of ‘passive’ follow-up of the cohorts, the rates of incident TB in the studies in Chapter 2 and Chapter 6 are overestimated, because we assumed the number of person years follow-up based on the initial cohorts, and did not correct for persons leaving the cohort either by leaving the country of through mortality. This limitation is most relevant for the study into the impact of preventive treatment of LTBI. However, we believe the influence of emigration and mortality to be limited in this group because of the overrepresentation of Dutch-born and younger age groups in our study cohorts; and these groups have low emigration and mortality rates (30).

**Conclusions and recommendations**

The studies in this thesis show how systematic monitoring and evaluation of routine TB interventions can provide the evidence to adjust the intervention and determine the target groups with more precision. This evidence enabled policy makers to reduce the number of immigrants and asylum seekers targeted for screening and to canalize the available resources to the interventions with the most impact on TB epidemiology. As such high quality surveillance and M&E are indispensable tools and essential components of the primary process of the PMHSs TB control units.

To gain more insight in the coverage and yield of tuberculosis screening of high-risk populations such as immigrants and asylum seekers, more information is needed on the size of the target groups. Public institutions serving the target population may provide useful aggregated information to estimate the coverage.

The cost-effectiveness of screening and screening algorithms is setting specific and subject to changes in target groups and costs. This is specifically the case for the test algorithms for LTBI, in (new) target groups with high rates of TST-positivity that require a high proportion of confirmation tests with IGRA. Therefore, cost-effectiveness calculations need to be repeated periodically, especially when policies are changed or new risk groups are targeted.

BCG-vaccination is the main contributor to missed opportunities for TB prevention among children. The overage of BCG-vaccination is not routinely monitored in the Netherlands, as is done for other child vaccinations. Inclusion of BCG-vaccination in the system for the national immunization program in children should be sought after to improve systematic monitoring of coverage and timeliness of the vaccination.

LTBI screening practices in target groups with a comparatively low or uncertain likelihood of exposure or high likelihood of remote exposure, such as health care workers and other professionals deemed at risk for exposure and travelers to endemic countries need to be critically revised, and the impact of LTBI screening of new target groups of migrants with a high risk to develop TB need to be explored.
References


