Evaluating the effectiveness of interventions for the prevention of tuberculosis in a low-incidence setting
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Surveillance of communicable diseases is regarded as the backbone of public health, in order to describe the epidemiological situation and serve as early warning system, to provide information for planning and to monitor the impact of interventions. This thesis explores how the use of routine surveillance and client registration data contribute to policy development in tuberculosis (TB) control in the Netherlands. This is shown through the description of five studies evaluating the effectiveness of the screening of immigrants, a new screening algorithm for the diagnosis of latent TB infection (LTBI) in risk groups, TB control in children in general and the effectiveness of the management of persons identified with LTBI.

Chapter 1 gives a general introduction to the thesis with basic information about TB, the epidemiology of TB and TB control efforts in the Netherlands as well as globally. In addition information on the goal and the objectives of TB surveillance is given, as well as a brief historic description of the organization of the TB surveillance system in the Netherlands with data collection using the Netherlands Tuberculosis Register (NTR).

Chapter 2 reports the results of the first monitoring and evaluation study on the effectiveness of entry screening for tuberculosis and biannual follow-up screening among 68,122 new immigrants in the Netherlands in 1998-2002. The aim of the study was to identify risk groups for TB among subgroups of immigrants and the coverage of follow-up screening. The definition of a risk group used in the Netherlands is a population group with a TB incidence of at least 50 per 100,000 population. The yield of entry screening was high, but overall coverage and yield of follow-up screening was low. The yield of follow-up screening was highest among immigrants with abnormalities on chest X-ray at entry (902 per 100,000 individuals). In immigrants with a normal chest X-ray, the incidence during follow-up was 9, 37 and 98 per 100,000 immigrants from countries with estimated tuberculosis incidences of <100, 100–200 and >200 per 100,000, respectively, while the coverage of the second to fifth screening round of the screening was 59, 46, 36 and 34% respectively. Based on recommendations following from this study, follow-up screening of immigrants with a normal chest X-ray from countries with an incidence of <200 per 100,000 individuals was discontinued in 2007.

The study reported in Chapter 3 aimed to assess the added value of interferon-gamma release assays (IGRAs) for Dutch TB control. IGRAs are novel, more specific, but more costly diagnostic tests for the diagnosis of latent tuberculosis infection (LTBI) compared to conventional tuberculin skin test (TST; Mantoux test). Public Municipal Health Services (PMHSs) contributed test results of TST and IGRA and background data on persons tested with an IGRA during 2008-2010 in a web-based database. We calculated the number of persons diagnosed with LTBI based on the result of TST only or on the result of the confirmatory IGRA and found that at least 60% of persons who would have been diagnosed with LTBI based on TST alone had a negative IGRA. Among those with a TST reaction below the cut-off for the diagnosis of LTBI, 13% had a positive IGRA. For 41% of persons tested with an IGRA after TST, the IGRA influenced whether or not an LTBI diagnosis would be made. Incremental costs of using IGRA after TST were balanced by the improved targeting of preventive treatment. We concluded that in low-prevalence settings like the Netherlands, using the more specific IGRAs as a confirmatory test avoids unnecessary treatment of persons with alleged LTBI while it enables diagnosis of LTBI in BCG-vaccinated high risk populations for TB. In accordance with
the results of this study, the CPT issued an official guideline for the diagnosis of LTBI recommending to use IGRA as a confirmatory test after TST in 2011.

The aim of the study reported in Chapter 4 was to explore possibilities for improved prevention of TB in children in the Netherlands. For this purpose we analyzed routine TB and LTBI surveillance data, described the overall trends in the period 1993-2012 and looked in particular into the occurrence of TB events among children that potentially could have been avoided through preventive measures in the period 2005-2012. We found an overall decline in TB incidence over the two decades from 3.6 per 100,000 in 1993 to 1.9 per 100,000 children in 2012. The decline was stronger among Dutch-born children compared to foreign-born children. In total 64% of childhood TB cases was detected through contact investigation or entry screening of immigrants. However, after arrival in the Netherlands, foreign-born children with TB were less likely to be detected through contact investigation. Ninety percent of children who started on TB treatment completed the treatment successfully. Thirty nine percent of children with TB disease who had been eligible for BCG-vaccination were not vaccinated. We concluded that the performance of TB control in the Netherlands can be considered to be good according to conventional indicators for the quality of TB control such as early case finding and treatment completion rates. Still, in 37% of children with TB there was at least one 'missed opportunity' for prevention. We recommended enhancing TB case finding and in particular preventive treatment of latent TB infection among migrant children, and improving the coverage of BCG-vaccination among eligible risk groups.

Chapter 5 describes the trends in target groups for LTBI screening, diagnostic methods and treatment regimens of 37,729 persons notified with LTBI in the NTR from 1993-2013, and explores independent risk factors and determinants for treatment initiation, treatment completion and adverse events. Two-thirds of the notified cases were detected through contact investigation. The numbers of persons with immunosuppressive disorders, elderly persons and foreign-born persons notified increased in recent years, due to policy changes and the introduction of IGRAs. In total, 77% started preventive treatment, of whom 82% completed preventive treatment and 8% stopped preventive treatment due to adverse events. Children and the immunosuppressed were more likely to start and complete preventive treatment, as were persons treated with rifampicin or rifampicin/isoniazid regimens. The latter groups were also 40% less likely to stop preventive treatment due to adverse events. We calculated that the estimated risk reduction on incident TB in the target population for LTBI management was 40-60%.

In Chapter 6 we studied TB incidence rates among 14,241 persons notified with LTBI during the period 2005-2013, stratified for case management and target groups for LTBI screening and analyzed associated risk factors. The overall incidence of TB for those completing PT, interrupting PT and not receiving PT was 187, 436 and 355 per 100,000 person years respectively for TB contacts and 63, 96 and 110 for other target groups. The rate ratio between TB contacts and other target groups was 3.1 (95%CI 2.0-4.9). In both groups TB incidence was highest in the first year after diagnosis. The rate ratio between those receiving and those not receiving PT reached statistical significance only in TB contacts. In the first year the rate ratio between contacts receiving PT and contacts interrupting PT or not receiving PT was 0.43 (95%CI 0.22-0.89) and 0.53 (95%CI 0.32-0.90), respectively. Age younger than 5 years was associated with a higher risk for progression to TB. The risk categories pre-
and post-exposure screening applicable to health care workers and travelers were independently associated with a lower risk for progression to TB and as was receiving full PT.

We concluded PT effectively reduces the risk for progression to TB among those with a high likelihood to develop TB. PT therefore should be targeted to persons with LTBI from risk groups with a comparable risk to develop TB as TB contacts.

In the general discussion in Chapter 7 the limitations of the studies and their implications for policy development were reviewed and discussed further. The study monitoring and evaluating the effectiveness of the screening of immigrants and consecutive reports on evaluations published in 2009 and 2013 led to adjustment of the target group for screening and changes in the Immigration Act. Based on the results of the study on the added value of IGRA, the approach to use IGRA as a confirmatory test after TST was endorsed in the professional guideline for LTBI diagnosis. However, reassessment of the cost-effectiveness of this test algorithm will be necessary when basic costs for the TST and IGRA change and new risk groups for LTBI screening are targeted. We showed that despite a high standard of the management of childhood TB and prevention of childhood TB, there is still room for further prevention of childhood TB cases, particularly through screening and preventive treatment of child immigrants for LTBI and improved implementation of BCG vaccination. These interventions were included in the objectives of the 2016-2020 National Plan for TB control.

The management of LTBI in the public health sector in the Netherlands is well monitored, and meets international standards. However, prioritizing target groups for LTBI screening to those with a similar risk of TB progression as TB contacts will have more impact on reducing the burden of TB in the Netherlands than including the conventional target groups with a formerly perceived high risk of exposure to TB, i.e. health care workers, other professionals and travelers.

In conclusion it can be stated, that analysis of the monitoring and TB surveillance data was instrumental to prioritize TB control efforts in the Netherlands to more clearly defined target populations with a high risk for TB.