



Ph.D. defence

Mycobacterium tuberculosis challenges in a low-burden country

Nordic tuberculosis and occupational tuberculosis in Denmark
assessed based on genotyping data

by Mathias Klok Pedersen

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Assessment committee:

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The defence will take place **Friday the 14th of September 2018 at 13:00**
in the Lecture Hall, building 43, Statens Serum Institut, Artillerivej 5, DK-
2300 Copenhagen S. The department will host a reception afterwards.



Abstract

Tuberculosis (TB) has been with mankind since ancient times. The airborne causative agent *Mycobacterium tuberculosis* (Mtb) was discovered by Robert Koch in 1882 and in recent decades DNA techniques have emerged, allowing us to perform distinct DNA fingerprinting of Mtb, known as genotyping. Mtb genotyping forms the foundation of the thesis comprising three studies.

In the **method study**, a new and alternative software procedure for analysing Mycobacterial Interspersed Repetitive Unit – Variable Number of Tandem Repeats (MIRU-VNTR) genotyping using BioNumerics® was described and validated, and supplemental instructions were provided to set-up and perform the analysis, which is now used routinely in Denmark.

In the **Nordic TB study**, TB incidence trends from 1990 through 2015 in Denmark, Sweden and Finland were compared, focusing on the native population, and cluster analysis were performed in two recent 2-year periods (2012-2013 and 2014-2015). The annual rate of change in TB incidence for the native population were significant slower in Denmark (-2.4%) than in Sweden (-6.1%) and Finland (-6.9%). Also, Denmark had higher clustering rates for natives, more native clusters with ≥ 4 cases and by far the largest native cluster, collectively suggesting that the TB control in Denmark is less effective than in Sweden and Finland.

In the **occupational TB study** all genotyped notified cases of presumed occupational TB in Denmark from 1992 through 2012 (N=130) were compared with a nationwide pool of more than 7.000 genotyped potential Mtb culture positive source cases. In that way, nearly half of the presumed occupational TB cases could be clarified as *confirmed* (N=12) or *unlikely* (N=46). The rest of the cases were categorized as *possible*; however, 15 cases could be categorized as *likely*. Six of the *confirmed* cases worked in health care, though the occupational risk for contracting TB in Denmark must be considered low.

Future studies should focus on a detailed exploration of the TB control programs in the Nordic countries, in order to identify possible specific differences in the setup and execution of TB control efforts. Tracking annual rate of change of TB incidence trends in subpopulations combined with up to date 2-year cluster analyses could serve as a benchmarking strategy in TB surveillance. An ambitious goal of accelerating the effort to reach the pre-elimination target of less than one case per 100,000 population in Denmark could be set. Though genotyping – or emerging newer techniques as Next Generation Sequencing (NGS) – provide an important supplement in analysing Mtb transmission, good epidemiological linkage information should still be a focus of any TB control efforts.