

TUBERCULOSIS - A GLOBAL EMERGENCY: AN OVERVIEW OF METHODS AND TOOLS TO CONTROL, UNDERSTAND AND TRACK THE TB EPIDEMIC WORLDWIDE

Christophe Demay, Thierry Zozio, Julie Millet, and Nalin Rastogi*

Institut Pasteur de Guadeloupe, France

Although tuberculosis (TB) is a preventable and treatable disease, it remains one of the leading infectious diseases worldwide. As a result of inadequate treatment, the proportion of patients with multiple-drug resistant TB (MDR-TB) is constantly increasing, and the extensively drug-resistant TB (XDR-TB) has become a new global threat. HIV infection is a potent risk factor for developing TB, and a significant increase in the number of HIV-infected persons in the last two decades has considerably increased the risk of rapid TB progression soon after infection or re-infection with *M. tuberculosis* in such patients.

In the above context, recent advances in the field of molecular typing are a new tool at the disposal of TB bacteriologists. This key-note lecture will focus on the determinants of cluster distribution and major advances in TB molecular typing. The initial development of DNA fingerprinting based on *IS6110*-RFLP was of great help to understand the epidemiology of this pathogen and to define priorities for an improved control of the disease. However, this method is today replaced by easier and faster PCR-based methods. One of these - the DR-locus Spoligotyping - is today widely used in clinical laboratories for molecular epidemiology, evolutionary and population genetics of tubercle bacilli. Recently, it was used to define major circulating clades of tubercle bacilli in an international database (<http://www.pasteur-guadeloupe.fr:8081/SITVITDemo>), which described 1939 shared-spoligotype patterns (STs), representative of 39,295 strains from 122 countries. Such data constitute a new tool to draw worldwide genetic prevalence maps of *M. tuberculosis* lineages. Other recent studies have also focused on single nucleotide polymorphisms (SNPs) and large sequence polymorphisms (LSPs)-based phylogeny of TB bacilli.

Although spoligotyping reflects the spread of the disease due to human migratory movements and may correctly identify "outbreak" episodes, it is not suitable when used alone for purely epidemiological investigations (it may over-estimate clustering of isolates), hence the need for 2nd line typing methods to know the exact rate of ongoing transmission. The PCR-based typing of Mycobacterial Interspersed Repetitive Units – variable number of tandem DNA repeats (MIRU-VNTRs) has provided this new tool. Used in association with spoligotyping, MIRU-VNTR typing has been adopted as the basis for large-scale, high-throughput genotyping of *M. tuberculosis* by CDC – Atlanta, and researchers alike. Consequently, the building and mining of polymorphic genetic databases provides with a new conceptual framework to study global TB epidemiology, and human demographical and TB co-evolutionary history. An updated in-house version under development at Institut Pasteur de Guadeloupe contains spoligotyping patterns from 65000 clinical isolates and MIRUs on 10000 isolates. New tools in development relate to: semi-supervised learning through computer-friendly rules for automatic labelling of TB lineages, SpoligoLogo graphic representation, automated MIRU pattern classification, as well as the development of tools for "Real-Time Tracking" of TB epidemics worldwide. Two potential new tools for extracting global TB data will be described, i.e., "The Dynamic Motion Viewer" – a web-based software to follow up TB epidemic dynamics overtime, and "The Snapshot Viewer" – permitting an exact snapshot at a given time point). The topic will be reviewed with regard to a recent example of an "Intercontinental XDR-TB Exposure Case" that attracted high media attention in May-June 2007.

* Nalin Rastogi, M.Sc., Ph.D., D.Sc., Head of the TB & Mycobacteria Unit, Institut Pasteur de Guadeloupe, Morne Jolivière, BP 484, F-97183 Abymes-Cedex, Guadeloupe, France ; phone +590-590-89 38 81, Fax +590-590-89 38 80 ; e-mail : nrastogi@pasteur-guadeloupe.fr