PhD defence Chakirath N'Dira Sanoussi

Mycobacterium tuberculosis complex strain diversity may impact disease presentation, diagnosis and outcome

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Institute of Tropical Medicine - Antwerpen

Dit is de omschrijving

Supervisor:

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Summary:

Tuberculosis (TB) is caused by bacteria of the *Mycobacterium tuberculosis* complex (MTBC) which comprises 7 human-adapted phylogenetic lineages, including the two *M. africanum* lineages (West-African 1 (L5) and 2 (L6)) that are geographically restricted to West and Central-Africa, and cause up to 40% of TB in West-Africa. This thesis aimed to increase the understanding of L5 epidemiology, diagnosis and genomic characteristics, and included a nationwide prospective cohort study in Benin, the country with the highest prevalence of L5 worldwide.

We identified numerous novel epidemiological associations that shed new light on this distinct MTBC member and suggested technical advances for improved unbiased TB diagnosis and molecular epidemiological studies. We found that L5 is under-represented in positive cultures and identified a decreased performance of the rapid MPT64-antigen-based assay for the identification of L5 as a MTBC member among positive cultures, likely due to an L5-wide non-synonymous SNP (I43N) in the *mpt64* gene. This risks misclassifying of positive L5 cultures as non-tuberculous mycobacteria. To overcome the culture bias observed, direct spoligotyping was used for lineage determination. The countrywide distribution of lineages differed significantly by patient's treatment history, with *M. africanum* present in 39.2% of new and 26.3% of previously-treated patients (31.1% and 21% respectively for L5 alone). In Cotonou, over 10 years, the L5 prevalence among new patients significantly declined by 9.4 % (1.2-17.6) as did L1, while the L4 prevalence increased by 16% (7.4-24.6), and the L6 prevalence remained similar.

To facilitate such multicentric studies/surveys, cetylpyridinium chloride, OMNIgene.SPUTUM and ethanol were compared for up to 28-day storage of sputum in ambient temperature, with an algorithm proposed to help the user in the choice.

Using comparative genomics, we identified differences in gene content not only between L5 and the currently used *M. tuberculosis* reference genome H37Rv (L4), but also among L5 strains (complete genomes from Benin, Gambia, Nigeria). Some genes were absent in L5, and based on their function, can partly explain the reduced growth in culture and other suggested characteristics of *M. africanum*.

In conclusion, direct genotyping should be used for MTBC population structure studies, and the algorithm for TB diagnostics testing in *M. africanum*-endemic countries could be improved, favoring direct diagnostics for unbiased results. The high within-L5 gene content variability suggests the pangenome of MTBC may be larger than previously thought, implying a reference-free *de novo* genome assembly approach may be preferable over the currently used H37Rv-based genome analyses.

Please register for the PhD defence before Thursday 3 October via mail to Karin Janssens. Please subscribe before 2 October in the interest of organization of the reception: kjanssens@itg.beâ€‹.