PhD defence Bassirou Diarra

Tuberculosis in Mali: diagnostic, phylogenetic and treatment challenges

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Institute of Tropical Medicine - Antwerpen

Dit is de omschrijving

Supervisor:

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Summary:

Drug-resistance is threatening the global control of tuberculosis (TB), the leading infectious cause of death worldwide, with incomplete understanding of predictors of poor treatment outcome. First-line TB drugs are more powerful and less toxic compared to most second-line drugs, further stressing the importance of early identification of rifampicin-resistant (RR) TB and preventing the transmission of de novo resistance. If feasible, WHO recommends “universal drug-susceptibility testing”, i.e. the search and identification of RR among new TB patients.

As universal drug-susceptibility testing is not yet implemented in Mali, we conducted a cohort study in Bamako to detect RR-TB early on during first-line treatment, and monitor RR-TB treatment. As conventional microscopy by either Ziehl-Neelsen or auramine is less sensitive, and does not distinguish between live and dead bacilli, mycobacterial culture is required for treatment monitoring. As an alternative to culture, which is not widely available, we applied fluorescein di-acetate (FDA) vital stain for detection of live mycobacteria in monitoring treatment success. Moreover, we estimated the population structure of mycobacterial strains circulating in Bamako, and determined clinical characteristics and outcome by lineage.

Our data shows that TB patients in Bamako present with a high bacillary burden, thus with advanced disease. Increased sensitization of the population about TB symptoms and training of clinicians may contribute to earlier diagnosis and treatment initiation. Among new TB patients, the level of primary RR was moderately high at 2.6% (95% CI: 1.7-3.7). All RR were caused by mutations within the RR determining region of the *rpoB* gene, suggesting that the rapid Xpert MTB/RIF assay serves the diagnostic algorithm well.

A high proportion (64%) of auramine-based treatment failures were FDA negative, reflecting continued expectoration of death bacilli. However, FDA was insufficiently able to identify early RR-TB or predict culture-confirmed treatment failure.

Regarding drug-resistant TB, we identified multiple challenges, including evidence of nosocomial transmission, low coverage of monthly monitoring and attrition. Neither HIV nor diabetes mellitus were identified as risk factors for acquiring drug-resistance.

As for circulating mycobacterial strains, we found that all first-six lineages of human importance were represented in Bamako, in addition to 0.8% *M. bovis*. The most widely represented lineages were Lineage 4 (Euro-American) (57%), and Lineage 6 (*M. africanum)* (22.9%). Lineage 6-diseased patients - compared to Lineage 4 - showed slower disease progression, higher smear-microscopy grades, and slower smear conversion by auramine and FDA. Hence, more efficacious treatment regimens are needed for Lineage 6 patients.

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€‹.â€‹

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