PhD defence Mulualem Tadesse Jano

Improving the diagnosis of tuberculosis in hard to diagnose populations: Clinical evaluation of GeneXpert MTB/RIF and alternative approaches in Ethiopia

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University of Antwerp, Campus Drie Eiken - Wilrijk
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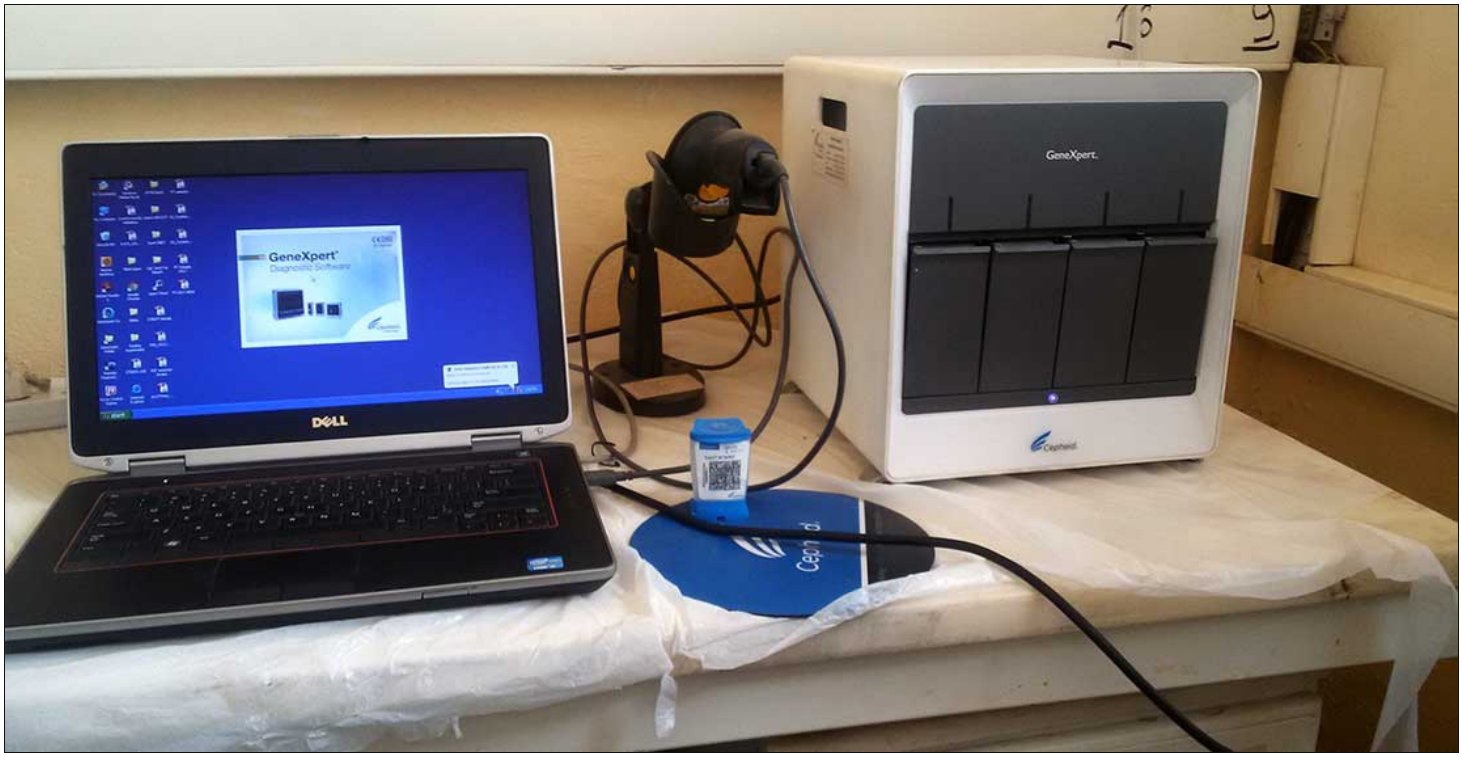

Dit is de omschrijving

Supervisors:

- Prof. Dr. Bouke de Jong (Institute of Tropical Medicine)
- Prof. Dr. Leen Rigouts (University of Antwerp, Institute of Tropical Medicine)
- Prof. Dr. Gemeda Abebe (Jimma University, Ethiopia)

Summary:

Enhancing tuberculosis (TB) detection rate requires evaluation and optimization of new diagnostic technologies as well as introduction of alternative approaches for improving the performance of current laboratory techniques. In this PhD thesis, we investigated such tools and alternative approaches for smear-negative pulmonary and extrapulmonary TB (EPTB) in Ethiopia.

Our first study evaluating the performance of the PCR-based Xpert®MTB/RIF assay for the diagnosis of smear-negative pulmonary TB indicates that Xpert MTB/RIF has modest sensitivity (63%) and excellent specificity (98%) for smear-negative culture-positive patients. Pre-treating smear-negative sputum with bleach and testing the pellet significantly improved Xpert MTB/RIF sensitivity, though this added value needs further study.

In three of our studies (paper II, III and IV) we evaluated the potential utility of conventional microscopy (with prior sample concentration), fluorescence microscopy and Xpert MTB/RIF for diagnosing TB lymphadenitis. Our findings concluded that routine use of conventional light microscopy on concentrated specimen and fluorescence microscopy can improve bacteriological diagnosis of TB lymphadenitis; yet these methods cannot be a standalone diagnostic test. Xpert MTB/RIF demonstrated better diagnostic performance than conventional diagnostic tools and substantially improved the diagnosis of TB lymphadenitis.

In study V, we comprehensively evaluated the diagnostic accuracy of Xpert MTB/RIF for different forms of EPTB using a composite reference standard. We found heterogeneous sensitivity of Xpert MTB/RIF among the specimen types (30% - 90%), with highest sensitivity for lymph nodes (90%), modest sensitivity for cerebrospinal fluid (53%) and lowest sensitivity for pleural (30%) and peritoneal fluids (32%). Our study showed that Xpert MTB/RIF is likely to be of greatest utility when testing lymph node specimens. The specificity of Xpert MTB/RIF was high across the different specimen types providing sufficient confidence for the clinician to initiate anti-TB treatment following a positive Xpert MTB/RIF result.

In the last study (study VI) , we explored the genetic diversity of circulating *Mycobacterium tuberculosis* complex (MTBc) strains isolated from 304 TB lymphadenitis patients in Southwest Ethiopia. We found that TB lymphadenitis in this region is caused by a wide diversity of MTBc strains with predominance of the Ethiopian specific sub-lineages within Lineage 4. Our analysis also revealed the presence of the typical Ethiopian Lineage 7 in Southwest Ethiopia, so far only identified in Northern Ethiopia. Moreover, the contribution of *M. bovis* in TB lymphadenitis infection is minimal, confirming earlier findings that in Ethiopia TB lymphadenitis arise from the same source as pulmonary TB, rather than from an external zoonotic source.

The findings of this doctoral thesis improve our understanding of different diagnostic methods and approaches for effective diagnosis of TB in hard to diagnose groups

such as EPTB and smear-negative PTB. Based on our findings, we recommend that Xpert MTB/RIF should be used as a replacement test for usual practice including conventional microscopy and cytology for testing lymph node specimens from patients suspected of having TB lymphadenitis in Ethiopia. While Xpert MTB/RIF has modest sensitivity in cerebrospinal fluid, it could still significantly improve diagnosis of TB meningitis as it provides rapid results. A negative Xpert MTB/RIF result on pleural or peritoneal fluid specimens does not exclude the diagnosis of EPTB and patients with a high clinical probability of EPTB should be started on anti-TB treatment. Future research should focus on evaluating potential impact beyond diagnostic accuracy such as patient outcomes, cost effectiveness, scalability and effects of programmatic implementations.