PhD defence Jean Claude Semuto Ngabonziza

Improving the diagnosis of rifampicin-resistant tuberculosis: programmatic aspects, diagnostic challenges, and molecular epidemiology

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Abstract

Tuberculosis (TB) remains the leading infectious disease cause of mortality globally. Resistance to rifampicin (i.e. the most powerful anti-TB drug) impedes optimal management of patients and TB control. Indeed, the majority of rifampicin-resistant (RR) TB patients remain undiagnosed and untreated, thus spreading resistant Mycobacterium tuberculosis complex (MTB) strains. In Rwanda the first RR-TB patients were diagnosed in 1989. However, adequate programmatic management of RR-TB started 15 years later, in response to an increasing prevalence and poor treatment outcomes. Stepwise interventions were implemented aiming at early diagnosis and appropriate treatment. First, the program expanded access to culture-based RR-TB detection. Second, rapid molecular tests, such as Xpert MTB/RIF, were implemented to swiftly diagnose RR-TB. My Ph.D. research showed a substantial reduction of delays in initiating RR-TB treatment from 175 days in 2006 to 5 days only in 2016. This reduction of delays decreased RR-TB related mortality from 30.8% in 2006 to 6.9% in 2016. Besides reduced mortality, I showed that such swift detection interrupted the spread of RR-TB, also that most RR-TB in Rwanda was caused by a single MTB clone that we named 'Rwanda rifampicin-resistant TB clone', or 'R3clone'. Through universal access to rapid rifampicin resistance testing, the R3clone population declined since 2014. However, the extensive use of Xpert MTB/RIF did not only yield positive effects. Ten years after its global rollout, my analysis showed very important pitfalls of Xpert MTB/RIF. As more and more patients were tested with Xpert MTB/RIF, a substantial proportion of patients were diagnosed early with paucibacillary disease. I showed that half of these patients diagnosed with RR-TB in fact had rifampicin-susceptible TB. The Xpert MTB/RIF software erroneously interprets insufficient DNA binding as evidence of resistance. Unfortunately, these patients were unnecessarily treated with a longer 'second line' treatment regimen with more toxic drugs. Based on my findings the National TB Programme in Rwanda changed the diagnostic algorithm, to further ascertain RR in patients with a paucibacillary sample before starting RR-TB treatment. Today, TB patients in Rwanda only receive second-line treatment if they really need it. Besides the challenges in diagnosing RR-TB, I identified a novel MTB lineage that we named lineage 8 (L8). The L8 is a sister clade to the known MTB lineages. Remarkably, the two L8 strains identified so far were resistant to key anti-TB drugs. L8 seems to be extremely rare and restricted to the Great Lakes region.