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Successful expansion of MDR-TB Clones in Northern Tunisia

Abstract: We carried out a whole genome sequencing (WGS)-based investigation on the emergence of a major multidrug-resistant tuberculosis (MDR-TB) outbreak in Tunisia caused by a lineage 4 (L4) *Mycobacterium tuberculosis* strain. Unlike the largest L4 MDR-TB outbreak that occurred in Argentina, the outbreak described herein evolved in a context strictly negative for HIV infection. To understand how MDR-TB strains emerge and spread, we explored the transmission dynamics of the *M. tuberculosis* Haarlem genotype in Northern Tunisia, where it caused a major outbreak affecting 48 individuals between 2001 and 2011. We ensured full coverage of the study region by analyzing all 250 *M. tuberculosis* clinical isolates displaying the Haarlem spoligotype signature. Using 24-loci MIRU-VNTR (multiple interspersed repetitive unit-variable-number tandem repeat) and WGS for 121 phylogenetically relevant isolates, we uncovered a high transmission rate among Haarlem isolates (83%) and identified a new minor MDR-TB cluster. Despite genetic divergence between the MDR-TB clusters, they evolved from a common drug-susceptible progenitor, most likely originating in 1886 (CI95% 1804-1927). Our findings provide evidence for the prominent role of incarcerated individuals in the onset of the outbreak and its spillover into the general population. By around 2008, the outbreak had progressed towards extensively drug-resistant TB (XDR-TB). In summary, our study highlights that even in the absence of HIV co-infection, the prison environment significantly contributes to the generation and transmission of highly transmissible M/XDR *M. tuberculosis* clones. These findings link the overall MDR-TB epidemics in Northern Tunisia to a single progenitor clone, a result that is both epidemiologically and fundamentally noteworthy.

Keywords: *M. tuberculosis*; MDR; Tunisia; L4.1.2.1; Incarceration

Biography: Dr. DEKHIL Naira is a postdoctoral researcher at the Institut Pasteur de Tunis, where she works in the Mycobacterial Typing and Genetics unit. She earned her PhD with a focus on the comparative and functional genomics of antibiotic-resistant strains of *Mycobacterium tuberculosis*, the causative agent of human tuberculosis (TB). Since 2017, she has been dedicated to the phylodynamic analysis of *M. tuberculosis* strains, contributing significantly to the understanding of their evolution and transmission. Dr. DEKHIL Naira is also an active member of Clinical Investigation Center at Institut Pasteur de Tunis.