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The *M. tuberculosis* F15/LAM4/KZN Strain is not more Virulent than the Globally Prevalent Beijing Strain during Early Infection of Alveolar Macrophages

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ABSTRACT

Mycobacterium tuberculosis, the causative agent of Tuberculosis (TB) is responsible for the highest mortalities globally from a bacterial pathogen. The *M. tuberculosis* F15/LAM4/KZN strain was implicated in the Tugela Ferry outbreak in the KwaZulu-Natal (KZN) province of South Africa in the early to mid-2000s. However, the impact of the F15/LAM4/KZN strain on cytokine and transcriptome profiles of alveolar macrophages has not been explored to date. The current study aimed to elucidate macrophage responses to the F15/LAM4/KZN, Beijing and the laboratory H37Rv through multiplexing cytokines in the Bioplex pro human cytokine 27-Plex assay and transcriptome changes using RNA sequencing at 48 h post-infection. Differential gene expression induced by the strains in infected, relative to uninfected, cells was quantified by Hisat-Ballgown bioinformatics pipeline, together with Gene Ontology and Kyoto Encyclopedia of Genomes (KEGG) for downstream pathway enrichment analysis. The F15/LAM4/KZN strain induced significantly higher concentration levels of IL-1ra, IL-2, IL-8, TNF-α, GM-CSF, and IL6 compared to Beijing, H37Rv and the uninfected cells. The ability of F15/LAM4/KZN to induce low levels of pro-inflammatory cytokines (IL-1β, IL-5, IL-17, and IFN-γ) compared to Beijing allude to its ability to favor a Th1 response. Furthermore, the current study revealed differential gene expression in macrophages infected with various *M. tuberculosis* strains as follows: Beijing (2045), F15/LAM4/KZN (416), and H37Rv (171); with a subset of 69 genes that were commonly induced. Strain-specific molecular signatures were associated with cytokine-cytokine interaction pathways, chemokine signaling, and nucleocytoplasmic transport pathways for Beijing, F15/LAM4/KZN and H37Rv strains, respectively. The current study suggests that the F15/LAM4/KZN is not more virulent than the globally prevalent Beijing strain. Hence, its high transmission dynamics in the Tugela ferry outbreak may be linked to the drug resistance patterns within this strain family and other health care system challenges, rather than a failure to activate macrophages during early infection.

Keywords: *Mycobacterium tuberculosis*, Alveolar macrophages, Cytokines, RNA Sequencing, Transcriptome, Gene expression

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