

Title: Contribution of granuloma characteristics and antibiotic exposure to treatment outcomes in *Mycobacterium tuberculosis* infection

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Factors determining antibiotic efficiency during *M. tuberculosis* (Mtb) infection are not well understood, but include access to the pathogen as well as pathogen susceptibility to the drug. In vivo, Mtb resides in lung granulomas, roughly spherical collection of immune cells that immunologically constrains and physically contains bacteria. Low drug penetration into granulomas might result in suboptimal drug concentrations. However, experimental studies of drug concentrations within granulomas are limited. To study the effects of antibiotics on bacteria in granulomas, we expand our existing computational agent-based model of granuloma formation in the lung to include antibiotic dynamics, distribution and activity in the granuloma. Antibiotic dynamics are simulated by including 1) plasma pharmacokinetics (PK) (to account for absorption, distribution and elimination of antibiotics) 2) lung-tissue PK (to account for permeation of antibiotics into lung tissue, diffusion within lung tissue and penetration into host cells) and 3) pharmacodynamics (to account for antibiotic killing of bacteria). We model two first-line antibiotics, isoniazid (INH) and rifampicin (RIF), alone and in combination, and evaluate four dosing schedules recommended by the CDC. Intermittent dosing schedules are predicted to take longer to eliminate bacteria and have higher percentages of granulomas with bacteria remaining compared to daily dosing schedules. Outcomes for INH treatment are more sensitive to dosing frequency than for RIF treatment. For INH treatment, higher doses do not necessarily compensate for decreased dosing frequency even if the same cumulative drug exposure is maintained. Results provide insight into determinants of antibiotic treatment success or failure, and can suggest better use of available antibiotics.