ABSTRACT FACE PAGE

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2. Presenting Author's affiliation: __Purdue University_____
3. Presenting Author's title: __*Mycobacterium avium* Infection in the Lungs: an Agent Based Model for Exploring Early Infection Events
4. Presenting Author's email: _weathered@purdue.edu_____
5. Presenting Author's gender (optional): ___female_____
6. Presenting Author's race (optional): _____
7. Presenting Author's ethnicity (optional): _____
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   ✓ **Academia**
   o Industry
   o FederalEmployee/Contractor
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   o K-12student
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   ✓ **Graduate Student**
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    _Dr. Elsje Pienaar_____

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MYCOBACTERIUM AVIUM INFECTION IN THE LUNGS: AN AGENT-BASED MODEL FOR EXPLORING EARLY INFECTION EVENTS

[1]Catherine Weathered* and [1]Elsje Pienaar
[1]Purdue University, West Lafayette, IN, USA
Email: weathered@purdue.edu

INTRODUCTION: Mycobacterium avium complex (MAC), members of the nontuberculous mycobacteria family, are environmental microbes, capable of colonizing and infecting humans following inhalation of the bacteria. MAC-pulmonary disease is notoriously difficult to treat and prone to recurrence, and both incidence and prevalence have been increasing [1]. There are two types of MAC lung infection – fibrocavitary and nodular, with fibrocavitary much harder to treat, and with much lower cure rates, as low as 76% even with optimal treatment [2]. MAC are well known to form biofilms and diverse colonies in the environment. These biofilms have been shown to aid in epithelial cell invasion [3], cause premature apoptosis in macrophages [4], and inhibit antibiotic efficacy [5]. We hypothesize that both phenotypic diversity and biofilm formation are key to establishing and prolonging infections in the lung. To address these hypotheses, we developed a model that shows the interactions between bacteria, biofilm and immune cells as an agent-based model (ABM). This model allows us to explore both the intracellular scale (bacterial phenotypes and macrophage killing), and tissue scale (biofilm formation and epithelial invasion).

METHODS: We used Repast Simphony to develop a three-dimensional ABM of *in vivo* MAC colonization to infection within the first 14 days post-deposition. The grid represents a length of lung airway with a layer of mucus/epithelial lining fluid (ELF). Bacteria agents are divided into either sessile (slow-growing, within biofilm and less susceptible to antibiotics), or planktonic (more quickly growing but not protected by biofilm) phenotypes. Biofilm is represented by continuous variables in each grid compartment, with values corresponding to the amount of extracellular matrix produced by bacteria in that grid compartment. To represent the protective properties of biofilm, the amount of biofilm is inversely related to the likelihood of a macrophage phagocytosing bacteria from that biofilm. All bacterial agents also release a chemoattractant that is represented by continuous variables in each grid compartment, and that diffuses throughout the grid. Macrophages probabilistically follow this chemoattractant gradient. Macrophages can phagocytose bacteria, prioritizing planktonic bacteria (not within biofilms), which infect the macrophage. Infected macrophages then have a probabilistic chance of killing internal bacteria. Macrophages also accumulate "apoptotic signal" through exposure to biofilm and internal bacteria.

RESULTS: The model was parameterized through a literature search, test cases based on *in vitro* experiments and Latin Hypercube Sampling for unknown parameter values. We found that parameters affecting macrophage chemotaxis and recruitment have significant impact on the number of macrophages, but not on the number or distribution of bacteria. Initial parameters – the initial bacteria count, initial macrophage count, and ratio of planktonic to sessile bacteria - have lasting impacts throughout the simulation. Parameters that pertain to only one bacterial subpopulation (e.g. extracellular growth rates) are not significantly correlated with outcomes overall, because the composition of the bacterial populations varies so much between simulations. Finally, we have found that biofilm increases the number of bacterial cells that invade the epithelium, but in the absence of biofilm bacteria are able to persist in the airways. Higher biofilm levels also increase macrophage chemo-attractant production, death and recruitment. The most significant biofilm parameter is the amount that is deposited with bacteria in the lung upon initial exposure. Our simulations indicate that, based on *in vitro* data, once bacteria are deposited in the lung they cannot generate biofilm quickly enough to have a significant an impact.

CONCLUSIONS: We have developed a multiscale agent-based model that allows us to study the initial colonization and infection in MAC-pulmonary disease on both the cellular- and tissue level. Early results show that initial parameters have lasting effects on the outcome of the deposition. Further, we have found that biofilms are not necessary to establish fibrocavitary type of MAC infection. Future directions of this work include organization of the infection into nodules, adding drug pharmacokinetics and pharmacodynamics to better understand the role of biofilm in treatment efficacy.

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