COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Development Of A Mathematical Model Of Within-host Dynamics Of Illness Following Biological Agent Exposure

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The weaponized release of a biological pathogen on a population can result in serious medical and operational consequences. For a military population, these consequences can manifest as impacts to warfighter health and performance as well as overall unit strength. To mitigate these effects, it is important to assess both the medical and operational impacts of a biological pathogen release. In the past, ID50s and probit slopes have been used to model pathogen releases, and statistical distributions have been used to model symptom onset and severity. While these models are informative for casualty estimation and patient stream modeling, they do not capture individual variability or allow for expanding models into combined injury, comorbidity, and/or medical countermeasure frameworks. To address these shortcomings, Applied Research Associates, Inc. (ARA) is developing a physiologically based, high-fidelity mathematical model to provide descriptions of molecular and cellular components and their interactions as they relate to the complex pathophysiology associated with human response to biological pathogen exposure.

This presentation focuses on the initial development phase of the mathematical modeling framework that used inhalation of the facultative intracellular bacterium, Francisella tularensis, and the subsequent onset of pneumonic tularemia to build model components and establish an understanding of the salient features of immune response to biological agents and key differences that arise from each unique exposure. Because the eventual outcome of a tularemia infection is highly variant for low dose exposures and dependent on the result of the early interactions between the pathogen and the immune system, we developed a stochastic physiological model of the cellular dynamics and interactions/responses between the bacteria and the immune cells in the lung solved with a continuous time discrete state dynamic stochastic simulation algorithm, known as the Gillespie algorithm. This model captures the early stages of the infection and is linked to a systemic compartment, allowing a transition from the stochastic model to a deterministic model when the infection has progressed beyond its initial stage. Ultimately, this work will provide a flexible, agent-agnostic framework to address additional pathogens in the future. This modeling approach will also produce reliable predictions of progression of illness/injury, presentation of medical sign/symptoms (S/S), and adverse health outcomes.

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