Speaker Abstracts

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Development, use and refinement of Shigella controlled human infections

Background. Since 1946 the controlled human infection model (CHIM) for Shigella has been used to improve understanding of disease pathogenesis, describe clinical and immunologic responses to infection and as a tool for vaccine development. As the frequency and intent for use in product development and down-/up-selection increases, standardization and consistency in the methods utilized is necessary.

Challenges. As the frequency and sample size of controlled human infections with Shigella increase, there is a need to standardize methods, endpoints and sample collection. To date institutional and investigator variability has led to inconsistencies in model application and reported endpoints. Harmonization of the methods utilized is needed to minimize variability in the host, ensure consistency in inoculum preparation and refine clinical endpoints to account for the complex of signs and symptoms arising from experimental Shigella infection. These refinements may be integral to the future use of these models to support vaccine licensure.

Approaches. Several recent advancements have been attempted to standardize the Shigella challenge model ensure consistency in attack rates and disease characterization over time and across institutions. The first is the transition from utilizing freshly harvested plate-grown organisms to lyophilized lots of product that can be directly administered to minimize potential variability in administered doses and subsequently disease attack rates. Additionally, efforts to establish and standardize the primary endpoint for utilization across institutions has been an area of increased focus to ensure consistent assessments of preliminary efficacy in potential vaccine candidates. In addition to the primary endpoints, harmonizing secondary endpoints characterizing shigellosis severity will enable a more robust assessment of vaccine candidates. Many of these methods, in addition to consensus recommendations regarding sample collection and testing, have recently been published in a Clinical Infectious Disease supplement and will be detailed.

Conclusions. Refinement and harmonization of the Shigella human challenge model will ensure consistency in its use and application in early stage clinical trials of prototype Shigella vaccines and enhance our understanding of the host response to infection and potentially assist in the identification of immune correlates of protection.