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Developing and utilizing controlled human models of infection

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ABSTRACT

The controlled human infection model (CHIM) to assess the efficacy of vaccines against *Shigella* and enterotoxigenic *Escherichia coli* (ETEC) has several unique features that could significantly enhance the ability to test candidate vaccines. Despite increasing interest in these models, questions remain as to how to best incorporate them into vaccine development and how to maximize results. We designed a workshop focused on CHIM as part of the Vaccines Against *Shigella* and ETEC (VASE) Conference.

The workshop, using the World Café method, focused on; clinical outcomes, nonclinical outcomes and model standardization. Researchers with a variety of expertise and experience rotated through each focus area and discussed relevant sub-topics. The results of these discussions were presented and questions posed to guide future workshops.

Clinical endpoint discussions focused on the need for harmonized definitions; optimized attack rates; difficulties of sample collection and a need for non-stool based endpoints. Nonclinical discussions centered on evolving omics-based opportunities, host predictors of susceptibility and novel characterizations of the immune response. Model standardization focused on the value of shared procedures across institutions for clinical and non-clinical endpoints as well as for strain preparation and administration and subject selection.

Participants agreed CHIMs for *Shigella* and ETEC vaccine development could accelerate vaccine development of a promising candidate; however, it was also appreciated that variability in the model and our limited understand of the host-pathogen interaction may yield results that could negatively impact a suitable candidate. Future workshops on CHIM are needed to ensure the optimal application of these models moving forward.

1. Background

The experimental human challenge model has shown great promise as a tool to advance novel vaccine candidates by providing an assessment of vaccine efficacy in a highly controlled environment in which the inoculum dose is well-defined and all the signs and symptoms of disease can be well described and managed [1]. The utility of the human challenge model was demonstrated through the ability of an oral cholera vaccine, Vaxchora™ (Paxvax, Redwood City, CA) to be licensed by the U.S. Food and Drug Administration (FDA) after demonstrating efficacy in a challenge model [2]. Other enteric vaccine candidates, including norovirus [3], have used the human challenge model to support continued vaccine development efforts. These studies highlight the potential utility of challenge studies in advancing vaccines to expanded field development and even licensure.

In contrast to studies with norovirus and cholera; experimental challenge studies for ETEC and *Shigella* have been limited principally to early phase vaccine development efforts and prototype vaccines to aid in down-selection decisions. While the potential utility of these challenge models is great, they also have inherent limitations including: variation in challenge organism preparation, prechallenge preparation of subjects (eg, fasting, stomach acid neutralization), clinical and immunological endpoints and consistency in model application over time and location. For example, as outlined by Porter et al., the attack rates as well as clinical endpoints for a single strain at a fixed dose can vary widely between studies [4]. The lack of standard clinical definitions between stud-

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ies can also influence the inter-study interpretation of results possibly leading to erroneous conclusions about candidate vaccines. Additionally, limited dose ranges of certain organisms, such as *Shigella sonnei* preclude a full appreciation of the dose-response curve and may limit applicability and yield inaccurate sample size estimates for vaccination/challenge trials [5]. This is further confounded by the inconsistent use of these models in vaccine development by different vaccine developers. To ensure the broadest and most consistent application of these models moving forward, efforts to refine and harmonize these models are warranted.

While historically CHIMs have focused on primary clinical outcomes and limited immunologic endpoints, recent technological advances and analytical capacity have enabled the introduction of systems biology approaches to understand the host-pathogen-environment relationship. As has been outlined by others; transcriptomics, proteomics, metabolomics and other 'omics' based approaches have been pushed to the forefront of vaccine discovery efforts [6]. The potential utility of these novel techniques to refine our understanding of host-pathogen-environment interaction to include host susceptibility, protective immune profiles, response to infection and expression of virulence factors in the human challenge model is intriguing. However, these methods have not been broadly applied in vaccination/challenge studies for *Shigella* or ETEC.

In an attempt to guide future use of the experimental human challenge model for enteric pathogens, and in particular ETEC and *Shigella*; we conducted a workshop as part of the first Vaccines Against *Shigella* and ETEC (VASE) Conference. The intent of the workshop was to assemble a heterogeneous group of researchers with varied perspectives and experiences in the development and utilization of the human challenge model to harness collective knowledge about how best to advance the application of the human challenge model for *Shigella* and ETEC.

2. Methods

The workshop was developed under a framework of the World Café method for collaborative learning [7]. To that end, participants were randomly assigned to one of three tables which covered the following topic areas: (1) clinical endpoints, (2) non-clinical endpoints, (3) model standardization. Each group was given 20 min to discuss a question within the topic area. Participants openly discussed and documented their discussion. Facilitators were assigned to each topic area to initiate conversation, encourage engagement of all workshop participants and document discussions to link ideas. At the completion of a session, each participant moved to a new table and a unique topic area of conversation. This process was repeated until all participants had focused on a question in each of the topic areas. Randomly assigned groupings were ensured by the provision of study cards that assigned people to one of 6 potential sequences. The facilitator remained at a single table throughout the process to enable cross-pollination of participant ideas and provide a link to what had been previously discussed.

The three questions being considered within each topic area are included in Table 1. Upon completion of the round table discussions, participants gathered for a presentation by each of the facilitators. A presentation on the groups' thoughts and responses to the posed questions were reviewed and discussed with all participants of the meeting. Additional comments and considerations were solicited from all attendees of the meeting in order to expand upon the knowledge gained and ensure a broad spectrum of thoughts and ideas.

3. Results

3.1. Clinical outcomes

There was significant discussion regarding whether "infection" or "disease" was the most important outcome for experimental enteric infection models. For this discussion, "infection" was agreed to be evidence of the organism in the subject (by culture, PCR or possibly immune response) while "disease" was considered as "infection with symptoms". There was consensus that preventing infection would be the highest goal for a vaccine but a more realistic and practical goal would be disease prevention. This was felt to be particularly important in the endemic setting where "infection" would be unlikely to be detected as people would not seek medical care without symptoms.

Additional discussions centered on the difference in the populations utilized for controlled human infection models compared to disease endemic populations. Of particular discussion was that participants in human challenge models are often heterogeneous in terms of racial, ethnic and socioeconomic background. This heterogeneity meets the expectations of the US Code of Federal Regulations in terms of "equal selection of subjects"; however, scientifically this diversity may translate to an array of outcomes that differ from those experienced by endemic populations. Unfortunately, despite extensive discussion, there was no consensus as to how a more homogeneous population could be utilized in experimental infection models.

The target disease rate also was a matter of considerable debate. Current challenge models of ETEC and *Shigella* have disease rates in the range of 70–75%. While some participants thought the optimal goal would be to have 100% of the subjects develop disease, numerous concerns were raised. The first was that a universal disease attack rate likely does not accurately reproduce the findings of an endemic setting. Additionally, lower vaccine efficacy estimates may result in the setting of aberrantly high disease rates due to

Table 1
Discussion questions within each topic area.

Topic area	Discussion questions
Clinical outcomes	What attributes of clinical outcomes in human challenge studies would help better predict positive impact in endemic settings? What value have clinical outcomes demonstrated in advancing enteric vaccines to the end goal of licensure or prequalification is licensure/prequalification the end goal for all? What are the main challenges limiting the application of the best clinical outcomes in the human challenge model?
Non-clinical	What nonclinical outcomes are currently missing or lacking that would facilitate identification of immune correlates/surrogates and guide candidate down selection? What currently used non-clinical outcomes provide critical information to help advance the field of vaccinology? How can we advance from currently utilized non-clinical outcomes to those that would transform enteric vaccine trials?
Model standardization	How would standardized methodologies and outcomes best be developed and disseminated? What are key features of a challenge model that would ensure constant clinical and nonclinical outcomes across time and space? Should human challenge models be utilized for vaccine candidate down selection?

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