Establishment of a Shigella Sonnei Human Challenge Model in Thailand

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**Background:** Shigella is a major causative agent of dysentery which is an important health problem in children in developing world, expatriates and travelers. Shigellosis is characterized by passing of frequent loose stool with mucous and blood which is usually accompanied by systemic illnesses e.g. fever, abdominal pain. While vaccines against shigellosis are ready for testing, protective immune responses against shigellosis still have not been clearly defined. An establishment of a safe and reliable human challenge model of shigellosis for vaccine evaluation is strongly needed.

**Methods:** We conducted an inpatient human challenge trial of \(S.\) sonnei in Thai adult volunteers to define a challenge dose of \(S.\) sonnei that will cause clinical disease, as defined by fever and diarrhea/dysentery, in 70% of volunteers. Three groups of 12 volunteers were orally challenged with wild type \(S.\) sonnei strain 53G at 100, 400 or 1600 cfu, respectively. Volunteers were followed to evaluate clinical symptoms, shedding, immune responses and adverse events. Volunteers were treated with ciprofloxacin on 120 hours after challenge. Out patient follow up visits were scheduled on Day 14 and Day 28 and a telephone visit was made on Day 42.

**Results:** The first group challenged with 93 cfu had 6/12 (50%) had dysentery where 3/12 (25%) also had fever. \(S.\) sonnei was detected in stool from half of the volunteers. Seven volunteers had IgG seroconversion against \(S.\) sonnei LPS. The second group challenged with 440 cfu had no clinically significant differences from the first group; 6/12 had diarrhea/dysentery where 1/12 also had fever, 8/12 had \(S.\) sonnei detected in stool and 7/12 had IgG seroconversion. In the third group challenged with 1680 cfu, 9/12 (75%) had dysentery where 3/12 (25%) also had fever. All except one volunteer (92%) excreted \(S.\) sonnei in stools. No clinically significant adverse events were reported from all 3 groups.

**Conclusion:** This is the first Shigella human challenge study conducted in a developing country. Although the desired clinical disease outcome of 70% was not achieved at any of the 3 challenge doses, we could demonstrate clinical dysentery in 75% of volunteers and 92% colonization of bacteria at the highest challenge dose of 1680 cfu of \(S.\) sonnei 53G. Clinical signs and symptoms of shigellosis are apparently much less severe in Thai volunteers than what was previously reported in U.S volunteers even at a 4-fold higher dose. Populations in endemic area with possible early and consistent exposure to the organism or related organisms may require higher infective doses and show milder clinical responses to Shigella infection.