Salmonella enterica serovar *Typhi* induces increased mucosal permeability and elicits a strong epithelial pro-inflammatory response ameliorated by vaccine candidates *in vitro*.

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Background: *Salmonella* species are a major cause of food poisoning and can induce a broad spectrum of diseases from mild diarrhea to typhoid fever. The World Health Organization estimates that 16 million cases of typhoid fever occur annually, resulting in ~600,000 deaths**.** Infection is initiated in the intestinal tract, and severe disease causes widespread destruction of the intestinal mucosa.

Aim: to study the effects of wild-type *Salmonella typhi* and vaccine strains, CVD 908-*htrA* and CVD 909, on the intestinal barrier function and cytokine production.

Methods: Enterocyte-like cell line, Caco2, was inoculated with wild-type *Salmonella typhi* and vaccine strains to evaluate initial host-pathogen interactions and the effect of exposure and colonization of these strains on mucosal barrier function. Changes in epithelial permeability were recorded and pro-inflammatory cytokines interleukin-8 (IL-8), interleukin-6 (IL-6) and TNF-α were measured in culture supernatants.

Results: Caco2 cells infected with wild-type Salmonella enterica serovar *Typh*i exhibited marked changes in tight junction proteins organization, an increase in the paracellular flux of dextran, and a rapid decrease in transepithelial electrical resistance (TEER) as early as 4h post-infection. Cell viability tests showed that barrier function disruption was not associated with cell death caused by bacterial infection.
S. typhi induced production of IL-8, IL-6 and TNF-α. Infection of Caco2 cells with the new oral vaccine strains, CVD 908-*htrA* and CVD 909, showed that both strains, but in particular CVD909, elicits immune response with minimal disruption of the barrier integrity, and hence offers reason for optimism for vaccine development.

Conclusions: *Salmonella typhi* causes specific and transient intestinal mucosal epithelial events, including changes in TEER and cytokine production that seem to be ameliorated by the engineering of specific vaccine candidates.