

Colonization factors among enterotoxigenic *Escherichia coli* isolates from children with moderate-to-severe diarrhea and from matched controls in the Global Enteric Multicenter Study (GEMS)

Vidal, Roberto M.

Muhsen, Khitam

Tennant, Sharon M.

Svennerholm, Ann Mari

Sow, Samba O.

Sur, Dipika

Zaidi, Anita K.M.

Faruque, Abu S.G.

Saha, Debasish

Adegbola, Richard

Hossain, M. Jahangir

Alonso, Pedro L.

Breiman, Robert F.

Bassat, Quique

Tamboura, Boub

Background: Enterotoxigenic *Escherichia coli* (ETEC) encoding heat-stable enterotoxin (ST) alone or with heat-labile enterotoxin (LT) cause moderate-to-severe diarrhea (MSD) in developing country children. The Global Enteric Multicenter Study (GEMS) identified ETEC encoding ST among the top four enteropathogens. Since the GEMS objective was to provide evidence to guide development and implementation of enteric vaccines and other interventions to diminish diarrheal disease morbidity and mortality, we examined colonization factor (CF) prevalence among ETEC isolates from children age <5 years with MSD and from matched controls in four African and three Asian sites. We also assessed strength of association of specific CFs with MSD. Methodology/Principal

findings: MSD cases enrolled at healthcare facilities over three years and matched controls were tested in a standardized manner for many enteropathogens. To identify ETEC, three *E. coli* colonies per child were tested by polymerase chain reaction (PCR) to detect genes encoding LT, ST; confirmed ETEC were examined by PCR for major CFs (Colonization Factor Antigen I [CFA/I] or Coli Surface [CS] antigens CS1-CS6) and minor CFs (CS7, CS12, CS13, CS14, CS17, CS18, CS19, CS20, CS21, CS30). ETEC from 806 cases had a single toxin/CF profile in three tested strains per child. Major CFs, components of multiple ETEC vaccine candidates, were detected in 66.0% of LT/ST and ST-only cases and were associated with MSD versus matched controls by conditional logistic regression ($p < 0.006$); major CFs detected in only 25.0% of LT-only cases weren't associated with MSD. ETEC encoding exclusively CS14, identified among 19.9% of 291 ST-only and 1.5% of 259 LT/ST strains, were associated with MSD ($p = 0.0011$). No other minor CF exhibited prevalence $\geq 5\%$ and significant association with MSD. Conclusions/Significance: Major CF-based efficacious ETEC vaccines could potentially prevent up to 66% of pediatric MSD cases due to ST-encoding ETEC in developing countries; adding CS14 extends coverage to $\sim 77\%$.