Etiology and adverse clinical consequences of moderate-to-severe diarrhea among children under five in three sub-Saharan African countries post-rotavirus vaccine introduction: The Vaccine Impact on Diarrhea in Africa (VIDA) Study

KL Kotloff[1,2], MJ Hossain[3], JCM Jones[3], SMA Zaman[3], H Badji[3], M Antonio[3], AM Keita[4], D Sanogo[4], B Tamboura[4], SO Sow[4], A Traore[4], R Omore[5], JB Ochieng[5], A Roose[1,2], J Verani[6], M-A Widdowson[6], J Tate[7], U Parashar[7], D Nasrin[1], I Kasumba[1], WC Blackwelder[2], H Powell[1,2], M Tapia[1,2], E Houpt[8], J Platts-Mills[8], and SM Tennant[1]

[1]Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, Maryland, United States of America, [2]Department of Pediatrics, University of Maryland School of Medicine, Baltimore, Maryland, United States of America, [3]Medical Research Council Unit The Gambia, Banjul, The Gambia, [4]Centre pour le Développement des Vaccins du Mali (CVD-Mali), Bamako, Mali, [5]Kenya Medical Research Institute/Center for Global Health Research (KEMRI-CGHR), Kisumu, Kenya, [6]Division of Global Health Protection, Kenya Office of the US Centers for Disease Control and Prevention, Nairobi, Kenya, [7]Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

[8]Division of Infectious Diseases and International Health, University of Virginia, Charlottesville, VA, USA

Background

The 3-year Vaccine Impact on Diarrhea in Africa (VIDA) case-control study assessed changes in the overall etiology and adverse clinical consequences of moderate-to-severe diarrheal illness (MSD) following rotavirus vaccine (RVV) introduction in The Gambia, Mali and Kenya.

Methods

All sites introduced RVV ≥1 year before VIDA initiation. MSD cases (children with diarrhea (≥33 loose stools/24h), plus dysentery, sunken eyes, decreased skin turgor, IV rehydration, or hospitalization) were enrolled from health centres in 0-11, 12-23 and 24-59 m age groups. Randomly selected, diarrhea-free matched controls were enrolled from home. A stool sample collected at enrolment from all participants was tested for enteropathogens using qPCR. Pathogen-specific attributable fractions (AF) were calculated using conditional logistic regression, adjusting for other pathogens and including interactions with age group and site. We assessed vital status and computed height-for-age Z-scores (HAZ) at enrolment and at follow-up 50-90 days later. Linear growth from enrolment to follow-up among cases and controls was compared using a mixed effects model. We compared findings from VIDA to data collected before RVV introduction at these 3 sites using identical methodology as part of the Global Enteric Multicentre Study (GEMS).

Results

Overall, 4840 cases and 6213 controls were enrolled. Whereas rotavirus was the most important pathogen at all sites among 0-11 m olds during GEMS, in VIDA rotavirus no longer dominated; the AFs decreased by ~40-50% while the AFs of *Cryptosporidium, Shigella*, *Campylobacter*, and norovirus increased, with some site-to-site variation. Among 12-23 m and 24-59 m olds, the AF of rotavirus showed small decreases; *Shigella* generally predominated, and AFs of *Campylobacter*, *Cryptosporidium, H. pylori,* and heat stable toxin (ST)-containing enterotoxigenic *E. coli* generally increased. As in GEMS, after adjusting for demographic and socioeconomic characteristics, baseline HAZ and follow-up time, case and control HAZ scores were similar at baseline but became 1 standard deviation (SD) lower at 60 days and 1.5 SD at 90 days ($p < 0.001$). During this vulnerable period, 38 cases and 3 controls died (OR: 16.4 (5.1-53.2)).

Conclusions

Our findings suggest that although rotavirus has decreased in importance, child health continues to be harmed by an episode of MSD.