

# WASH and Vaccines

November 2016

Rotavirus vaccine seroconversion and potential interference from Environmental Enteric Dysfunction: A comprehensive evaluation of diarrhoea among immunized child populations in Zambia.



Dr Joseph Katema, former Minister of Community Development, Mother and Child Health, giving the first Rotavirus Vaccine to a child in Zambia

## BRIEFING NOTE

Written by:  
Roma Chilengi<sup>1</sup>  
Sophie Durrans<sup>2</sup>  
Erin Flynn<sup>2</sup>

<sup>1</sup> Centre for Infectious Disease Research in Zambia

<sup>2</sup> London School of Hygiene and Tropical Medicine

## Background

Diarrhoea is the second leading cause of death in children under five worldwide (Liu L, 2012). Rotavirus is well documented as the principal cause of severe and moderate diarrhoea. Current estimates from 2013 are that approximately 233 000 annual child deaths are attributable to severe rotavirus gastroenteritis (RVGE) (Tate et al, 2016). Despite this the contributions of many specific gut pathogens on the burden of diarrhoea in many low and middle-income countries remains unclear (Kotloff et al, 2013). While enteric pathogens are detected in children with diarrhoea, they are also commonly identified in children without diarrhoea in low and middle-income countries (LMICs).

Two rotavirus vaccines are currently marketed internationally and have been introduced into routine immunization schedules in high burden countries. A large number of randomized, controlled trials have shown that both vaccines are 80%-90% efficacious against severe RVGE in countries higher income countries- with very low child mortality; and 40% - 60% efficacious in lower income countries

with-high child mortality (Naylor et al, 2015). This relatively poor performance of live oral vaccines in these settings remains unexplained.

One possible explanation is the concept of Environmental Enteric Dysfunction (EED). This chronic condition is caused by repeated gut infections and gut dysfunction, resulting in intestinal inflammation, poor nutrient absorption and weaker vaccine immune response.

Understanding the role of pathogens on oral vaccine failure may help to explain why the rotavirus vaccine has low levels of effectiveness in high burden settings. Under SHARE phase II, the Centre for Infectious Disease Research in Zambia (CIDRZ) - uniquely situated at the forefront of diarrhoeal surveillance efforts in Zambia - will be conducting research to better understand this phenomenon. It has recently led studies to evaluate rotavirus vaccine effectiveness (VE) in the context of a newly introduced vaccine programme, clean water initiatives, sanitation and community education for prevention of diarrhoeal infections in children under five in Lusaka Province.

## Aims and Objectives

This study aims to simultaneously evaluate the viral, bacterial and protozoal aetiologies of moderate-to-severe diarrhoea in Zambian children under the age of five. Researchers will evaluate the presence of these pathogens among those with diarrhoea who have been immunized with the rotavirus vaccine and those who have not, as well as among a control group of children without diarrhoea.

### Objectives:

- To document the prevalence of 15 enteric pathogens (viral, bacterial, and protozoal) among children with moderate-to-severe diarrhoea and the influence of mixed enteropathogen infection on the clinical features and severity of symptoms.
- To determine prevalence of serological and stool markers of environmental enteric dysfunction (EED).
- To determine the effect of EED on rotavirus vaccine seroconversion.
- To document the frequency of diarrhoea causing pathogens among rotavirus vaccine immunized infants as compared to non-immunized infants .
- To assess the association between environmental conditions and the risk of infection/co-infection as well as vaccine seroconversion.

## Project Overview

Firstly, the study will generate descriptive data on aetiology of diarrhoea in Zambian infants in the post rotavirus vaccine immunization era. Descriptive tables will show the absolute and relative frequencies of the pathogens isolated from the samples. Secondly, researchers aim to generate the first description of markers of EED in children from both stool and serum samples in Zambia. Thirdly, the study will estimate the attributable or preventable fraction among the vaccine exposed children, using odds ratio as a proxy for the risk ratio of diarrhoea.

### Study Design

This study will use existing data and samples collected from two previous studies at CIDRZ: an ongoing cohort study on 'Causes of rotavirus vaccine failure in Zambian infants' (ROVAS) and a prospective study 'A Comprehensive Assessment of Diarrhoea and Enteric Disease Management in Children (ACADEMIC)'.

Using paired serum samples from the ROVAS study, this project will test the infant serum at baseline to evaluate for several known serological markers of EED. Additionally, researchers will conduct molecular diagnostic testing on stool samples from the ACADEMIC study, including both samples from children with diarrhoea as well as asymptomatic control samples. They will also measure novel biomarkers of EED.

### Laboratory Assays

The study will use several known tests to evaluate serological markers of EED. Using these methods three parameters will be examined: the breakdown of the intestinal barrier, microbial translocation into blood, and presence of local intestinal inflammation. To evaluate gastrointestinal pathogens, the x-TAG Gastrointestinal Pathogen Panel test will be used for simultaneous detection of 15 enteropathogens in stool samples.

## Relevance and Uptake

While this study has relevance within Zambia it will also be important for the global evidence base on live oral vaccine performance. Importantly the results of this study will yield novel insights into the microbial ecology of diarrhoea in Zambia. Furthermore, it will provide pertinent information about the potential burden of poor WASH on children under 5 and future vaccine strategies.

To ensure the study findings are made widely available the principal investigator, with the support of SHARE, will disseminate preliminary and final results via global forums such as Stockholm World Water Week and UNC Water and Health Conference and directly to relevant teams in WHO and UNICEF. Within Zambia, project updates will be shared with relevant staff from the Ministry of Health. A series of papers

will also be submitted to peer reviewed journals to ensure the study findings are contributing to the global evidence base.

## Find out more

Sign up to the SHARE newsletter to keep up-to-date with this and other interesting projects: <http://bit.ly/1GrEEi8>.

## References

Kotloff, KL. et al (2013) Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *Lancet*. 2013 Jul 20;382(9888):209-22

Lui, L. et al. (2012) Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000 *Lancet* 379(9832):2151-61

Naylor, C. et al. (2015) Environmental Enteropathy, Oral Vaccine Failure and Growth Faltering in Infants in Bangladesh *EBioMedicine*. 2015 Nov; 2(11): 1759-1766.

Tate, J. et al (2016) Global, Regional, and National Estimates of Rotavirus Mortality in Children <5 Years of Age, 2000-2013 *Clinical Infectious Diseases* CID 2016:62 (Suppl 2), S96

---

## Contributors



This material has been funded by UK aid from the Department for International Development (DFID). However, the views expressed do not necessarily reflect the Department's official policies.

LONDON  
SCHOOL of  
HYGIENE  
& TROPICAL  
MEDICINE

