

## Community-acquired diarrhoea in a world with rotavirus vaccine: a glimpse into the future



Diarrhoea remains a leading cause of morbidity and mortality in young children around the world, with more than half a million children dying every year from diarrhoeal diseases.<sup>1</sup> In addition to its acute effects, diarrhoea can contribute to malnutrition, growth retardation, and cognitive impairment. A multifaceted approach is needed to combat this public health problem, and a better understanding of specific causative agents of diarrhoea will enable targeted prevention and treatment decisions.

In 2013, researchers from the Global Enteric Multicenter Study (GEMS)<sup>2</sup> reported data from seven low-resource countries on the incidence, cause, and adverse outcomes of moderate-to-severe diarrhoea in children from birth to 59 months. The authors of GEMS confirmed the large burden of moderate-to-severe diarrhoea and reported a significant association with linear growth faltering and death in the selected low-resource settings. Rotavirus was, unequivocally, the most common cause of moderate-to-severe diarrhoea in the first 2 years of life, while other pathogens, such as *Cryptosporidium* spp and heat-stable toxin-producing enterotoxigenic *Escherichia coli* (ST-EPEC), contributed significantly to mortality.<sup>3</sup>

In this issue of *The Lancet Global Health*, James Platts-Mills and colleagues<sup>4</sup> describe causes of diarrhoeal illness in

the Mal-ED study. By contrast with GEMS, which sought to characterise the diarrhoeal episodes most likely to contribute to childhood mortality—that is, moderate-to-severe diarrhoeal disease in children seeking care at health-care facilities—researchers in the Mal-ED study undertook intense community surveillance to record diarrhoea of any severity in the first 2 years of life.

Eight sites in South America, Africa, and Asia participated in the study. Investigators collected diarrhoeal and non-diarrhoeal stools in order to calculate the adjusted attributable fraction to estimate pathogen-specific burdens of diarrhoea. The study was impressive in the heterogeneity of sites, the completeness of sample collection, and the comprehensiveness of stool testing.

The pathogens most often associated with diarrhoea, in order of importance, were norovirus GII, rotavirus, and *Campylobacter* spp in children younger than 1 year, and *Campylobacter* spp, norovirus GII, and rotavirus in children aged 1–2 years, although there was considerable variation between sites. As with the GEMS study, several agents were commonly isolated but not associated with diarrhoea, including *Giardia* and enteroaggregative *E coli*.

The Mal-ED results further emphasise the importance of rotavirus as a cause of severe diarrhoea—rotavirus was the pathogen most often associated with severe diarrhoeal episodes in the first and second years of

Published Online  
July 20, 2015  
[http://dx.doi.org/10.1016/S2214-109X\(15\)00052-2](http://dx.doi.org/10.1016/S2214-109X(15)00052-2)  
See [Articles](#) page e564

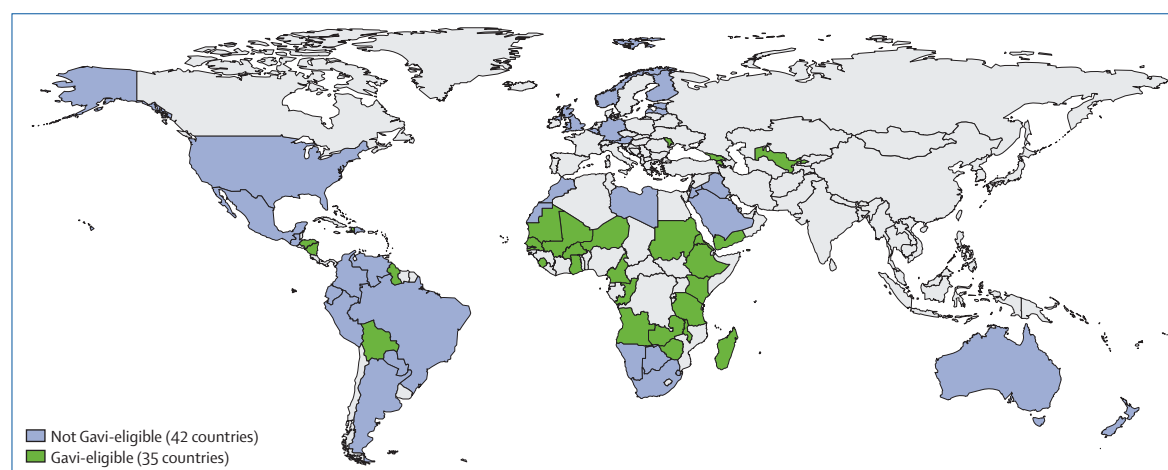


Figure: Countries that have introduced rotavirus vaccine to their nation immunisation programme, as of July 1, 2015

Figure adapted and used with permission from PATH<sup>6</sup>

life. The effect of rotavirus vaccination on findings was evident. In the five sites where rotavirus vaccines had not yet been introduced, rotavirus had the highest overall attributable fraction, whereas in the three sites where rotavirus vaccination had been introduced, rotavirus had only the fifth highest attributable fraction. Remarkably, in South Africa and Brazil, two countries that have introduced rotavirus vaccines, rotavirus was either not detected or not associated with diarrhoea in the first year of life. In Peru, the third site in the study to have introduced rotavirus vaccine, the attributable fraction was only 1.0 (95% CI 0.0–1.6) in the first year of life.

WHO has recommended rotavirus vaccines for all children since 2009.<sup>5</sup> The good news is that, as of July 1, 2015, 77 countries, including 35 eligible for support from GAVI, have introduced rotavirus vaccines into their national immunisation programmes (figure).<sup>6</sup> Studies to directly compare disease burden before and after vaccine introduction are already underway in Africa. Unfortunately, millions of children live in countries that have not yet included rotavirus vaccines in their national immunisation programmes. Platt-Mills and colleagues' results<sup>4</sup> should provide additional impetus for the remaining countries to introduce rotavirus vaccines, particularly those in sub-Saharan Africa and southeast Asia, where more than 80% of the rotavirus deaths in children under 5 years occur.

The introduction of rotavirus vaccines would be expected to lead to changes in the relative importance of other pathogens as causes of clinically important diarrhoea. For example, in the USA and some middle-income countries with the rotavirus vaccine, norovirus has replaced rotavirus as the most common agent identified in children hospitalised with acute gastroenteritis.<sup>7,8</sup> In the Mal-ED study, *Campylobacter* spp had the strongest association with diarrhoea in the first year of life in all three sites where rotavirus vaccines had been introduced. Yet, *Campylobacter* spp were not a prominent cause of moderate-to-severe diarrhoea in the GEMS study. Thus, further studies are needed to determine the most common causes of severe diarrhoea in low-resource settings after the introduction of rotavirus vaccines to allow planning of the most effective interventions to prevent and treat diarrhoeal illnesses in the future.

The increasing availability of molecular diagnostics promises higher detection rates of diarrhoeal

pathogens, especially when antibiotic administration impedes identification of bacterial agents with traditional diagnostic techniques. Nevertheless, the substantial variation by location, severity and season in the pathogens isolated, and the large proportion of diarrhoeal episodes with no identifiable causative agent, emphasises the need for generic, multifaceted approaches to the prevention and treatment of diarrhoeal diseases. The WHO/UNICEF Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD) addresses the critical need for coordinated and collaborative implementation of interventions.<sup>9</sup> The plan advocates for accelerated efforts to decrease the incidence of diarrhoeal disease—irrespective of the cause—through rotavirus vaccines, improved access to clean water, sanitation and hygiene, promotion of breastfeeding, and by improving access to zinc therapy and oral rehydration solution to improve health in the world's most vulnerable children.

\*Kathleen M Neuzil, Karen L Kotloff

Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD 21201, USA  
kneuzil@medicine.umaryland.edu

KN declares no competing interests. KLK receives funding from Merck for research related to rotavirus vaccines.

Copyright © Neuzil et al. Open Access article distributed under the terms of CC BY-NC-ND.

- 1 Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet* 2012; **379**: 2151–61.
- 2 Levine MM, Kotloff KL, Nataro JP, Muhsen K. The Global Enteric Multicenter Study (GEMS): impetus, rationale and genesis. *Clin Infect Dis* 2012; **55**(Suppl 4): S215–24.
- 3 Kotloff KL, Nataro JP, Blackwelder WC, et al. 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; **382**: 209–22.
- 4 Platt-Mills JA, Babji S, Bodhidatta L, et al. Pathogen-specific burdens of community diarrhoea in developing countries: a multisite birth cohort study (MAL-ED). *Lancet Glob Health* 2015; published online July 20. [http://dx.doi.org/10.1016/S2214-109X\(15\)00151-5](http://dx.doi.org/10.1016/S2214-109X(15)00151-5).
- 5 WHO. Meeting of the immunization Strategic Advisory Group of Experts, April 2009—conclusions and recommendations. *Wkly Epidemiol Rec* 2009; **84**: 220–36.
- 6 PATH. Country introductions of rotavirus vaccines. <http://sites.path.org/rotavirusvaccine/country-introduction-maps-and-spreadsheet/> (accessed July 2, 2015).
- 7 Koo HL, Neill FH, Estes MK, et al. Noroviruses: the most common pediatric viral enteric pathogen at a large university hospital after introduction of rotavirus vaccination. *J Pediatric Infect Dis Soc* 2013; **2**: 57–60.
- 8 Becker-Dreps S, Bucardo F, Vilchez S, et al. Etiology of childhood diarrhea following rotavirus vaccine introduction: a prospective, population-based study in Nicaragua. *Pediatr Infect Dis J* 2014; **33**: 1156–63.
- 9 WHO/UNICEF. Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD). Geneva: World Health Organization, 2013. <http://apps.who.int/iris/handle/10665/79207> (accessed May 17, 2015).