Tropical Medicine and International Health doi:10.1111/tmi.13040

VOLUME 23 NO 4 PP 425–432 APRIL 2018

Impact of rotavirus vaccination on rotavirus hospitalisation rates among a resource-limited rural population in Mbita, Western Kenya

Ernest Apondi Wandera[1,2], Shah Mohammad[1], Martin Bundi[2,3], James Nyangao[4], Amina Galata[1], Cyrus Kathiiko[1], Erick Odoyo[1], Sora Guyo[1], Gabriel Miring'u[1], Satoshi Komoto[5] and Yoshio Ichinose[1,2]

1 *Institute of Tropical Medicine, Kenya Research Station, KEMRI/Nagasaki University, Nairobi, Kenya*
2 *Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan*
3 *National Biosafety Authority, Nairobi, Kenya*
4 *Centre for Virus Research, KEMRI, Nairobi, Kenya*
5 *Department of Virology and Parasitology, School of Medicine, Fujita Health University, Toyoake, Japan*

Abstract

OBJECTIVES A two-dose oral monovalent rotavirus vaccine (RV1) was introduced into the Kenyan National Immunization Program in July 2014. We assessed trends in hospitalisation for rotavirus-specific acute gastroenteritis (AGE) and strain distribution among children <5 years in a rural, resource-limited setting in Kenya before and after the nationwide implementation of the vaccine.

METHODS Data on rotavirus AGE and strain distribution were derived from a 5-year hospital-based surveillance. We compared rotavirus-related hospitalisations and strain distribution in the 2-year post-vaccine period with the 3-year pre-vaccine baseline. Vaccine administrative data from the Unit of Vaccines and Immunization Services (UVIS) for Mbita sub-county were used to estimate rotavirus immunisation coverage in the study area.

RESULTS We observed a 48% (95% CI: 27–64%) overall decline in rotavirus-related hospitalisations among children aged <5 years in the post-vaccine period. Coverage with the last dose of rotavirus vaccine increased from 51% in year 1% to 72% in year 2 of the vaccine implementation. Concurrently, reductions in rotavirus hospitalisations increased from 40% in the first year to 53% in the second year of vaccine use. The reductions were most pronounced among the vaccine-eligible group, with the proportion of cases in this age group dropping to 14% in post-vaccine years from a high of 51% in the pre-vaccine period. A diversity of rotavirus strains circulated before the introduction of the vaccine with G1P[8] being the most dominant strain. G2P[4] replaced G1P[8] as the dominant strain after the vaccine was introduced.

CONCLUSIONS Rotavirus vaccination has resulted in a notable decline in hospital admissions for rotavirus infections in a rural resource-limited population in Kenya. This provides early evidence for continued use of rotavirus vaccines in routine childhood immunisations in Kenya. Our data also underscore the need for expanding coverage on second dose so as to maximise the impact of the vaccine.

keywords rotavirus, gastroenteritis, vaccine impact, Kenya

Introduction

Group A rotavirus (RVA) is the leading cause of severe childhood acute gastroenteritis (AGE) globally [1]. In Kenya, before the introduction of the vaccine, RVA was estimated to cause more than 3908 deaths [1], 3015 outpatient visits, and 279 hospitalisations per 100 000 children <5 years of age [2] and to cost the health care system US$10.8 million annually [3]. In 2009, two rotavirus vaccines, RotaTeq® (Merck & Co. Inc., USA), a pentavalent rotavirus vaccine (RV5) composed of five bovine-human reassortant strains including G types G1–G4 and P type P[8], and Rotarix® (GlaxoSmithKline Biologicals, Belgium), a monovalent rotavirus vaccine (RV1) composed of one attenuated human G1P[8] strain, were recommended for global use by WHO [4]. As of March 2017, 92 countries had introduced rotavirus vaccines, including 85 national, two ongoing phased, and five sub-national introductions [5]. With support from GAVI, Kenya introduced the two-dose RV1 into the national immunisation programme in July 2014. The vaccine is administered orally at 6 and 10 weeks of age, and the

goal is to protect more than 1.5 million children in the country from developing severe AGE [6].

After their global introduction, rotavirus vaccinations have had a remarkable impact in reducing the burden of severe childhood gastroenteritis, as demonstrated in several high- and middle-income countries in the Americas and Europe [7–10]. In some of these countries, rotavirus vaccinations have also resulted in the development of herd immunity among children who were not vaccinated and among older children and even adults who were not vaccine-eligible [11, 12]. Similarly, there is early evidence to suggest that these vaccines will have a significant impact in preventing and reducing the health burden of severe AGE in developing countries in Africa, despite their lower efficacy in clinical trials in these settings. Post-vaccine introduction studies in these African countries have reported reductions in all-cause gastroenteritis ranging between 18% and 65% [13–20]. Proportions in rotavirus-associated hospitalisations have been shown to decline at rates ranging from 24% to 56%, with most reductions being pronounced in children aged <1 year [17–19, 21–24]. It is noteworthy that data from Botswana and Zambia have indicated a decline of 27–48% in in-hospital mortality from gastroenteritis at various sentinel hospitals [14, 18]. In Kenya, rotavirus vaccination is predicted to avert 60 935 undiscounted deaths and 216 454 hospital admissions among children aged <5 years and will permit the government to avoid health care costs of US$ 30 million and a cost per disability-adjusted life-year (DALY) of US$ 38 million over the first 20 years of its use [25].

Nonetheless, data on the real-world impact of rotavirus vaccinations, in terms of preventing and reducing the health burden of severe childhood diarrhoea in Kenya, are lacking. Moreover, the variation in efficacy by gross domestic product [26] underscores the importance of monitoring the impact of rotavirus vaccinations in low-income settings during routine programmatic use, where the actual performance of a vaccine may differ from the optimal conditions of clinical trials. Thus, in this study, we report on the impact of rotavirus vaccination on rotavirus-specific AGE and strain distribution in a rural, resource-limited population in Western Kenya 2 years after the vaccine had been introduced into the national immunisation programme.

Materials and methods

Study setting

We conducted active hospital-based surveillance for rotavirus gastroenteritis in paediatric wards of the Mbita Sub-county Hospital (MSH) from August 2011 to July 2016. MSH is run by the government of Kenya and is the main referral hospital in Mbita sub-county. The hospital has 20-bed general wards and 10 paediatric cots and generally serves populations from Mbita sub-county and its environs. Mbita is a rural sub-county of Homa Bay County on the shores of Lake Victoria in Western Kenya, about 400 km west of Nairobi. It is a poor-resource setting: the county's GDP of 0.3 billion USD accounts for only 1.2% of national GDP [27]. Less than 25% of the adult population in the sub-county has employment with a regular wage; the majority of the population depends on subsistence farming, small-scale businesses, fishing, and keeping domestic animals [28]. According to the 2014 Kenya Demographic and Health Survey (KDHS), only 53.7% of children aged 12–23 months in this area were fully immunised [6]. Routine rotavirus vaccinations were rolled out in Mbita sub-county in July 2014. Thus, in our surveillance, the 3 years from August 2011 to July 2014 were defined as the pre-vaccine period, while the 2 years from August 2014 to July 2016 were defined as the post-vaccine period. Study subjects were infants and young children below the age of 5 years who were hospitalised at MSH with severe AGE and had experienced an episode of three looser-than-normal or watery stools within a 24-h period for not more than 7 days with or without episodes of vomiting [29]. The children either came directly from the community or were referred from peripheral health centres and dispensaries. Decisions on investigations, hospitalisation, and treatment were at the discretion of the clinicians attending to the children.

Ethical considerations

This study was approved by the Kenya Medical Research Institute/National Ethical Review Committee (SSC No. 1323). Written informed consent was obtained from the caregivers of all participating children after the nature and possible consequences of the study had been fully explained.

Sample collection

Demographic and clinical data were collected from the children who met all of the inclusion criteria using a pathological investigation form adapted from the WHO generic protocol for rotavirus surveillance [29]. After written informed consent was granted, faecal samples consisting of either whole stool or rectal swabs were collected in clean sterile containers within 48 h of admission. Each sample was labelled with the date of collection and a sample number was assigned. The

samples were stored at 4 °C at the hospital before being transported to the Nagasaki University, Institute of Tropical Medicine, Kenya Research Station where they were stored at −80 °C until processed.

RVA detection

About 1 ml aliquot of a 10% faecal suspension was prepared for use in an Enzyme-Linked Immuno-Sorbent Assay (ELISA) and RNA extraction. Briefly, about 1 g of stool sample or 100 μl of a rectal swab suspension was added to 1 ml of 0.01 M phosphate-buffered saline (PBS) (pH 7.2). The mixture was vortexed vigorously for 40 s and then centrifuged at 11200 × g for 5 min. The supernatant was transferred to new tubes and stored at −30 °C until used. Specimens from the 10% faecal suspension were tested for RVA antigen by ELISA as described previously [30]. Aliquots of all specimens were stored at −80 °C for further testing.

G and P genotyping

RVA double-stranded RNA was extracted from 10% faecal suspensions with ISOGEN-LS (Nippon Gene Co., Ltd., Toyama, Japan) according to the manufacturer's protocol. The extracted RNA was reverse-transcribed into the complementary DNA (cDNA) using ReverTra Ace® qPCR RT Kit (Toyobo Biotechnology Co., Ltd., Japan). The cDNA was then amplified in a two-step multiplexed seminested reverse transcription-polymerase chain reaction (RT-PCR) to determine the G and P genotypes of the RVA strains using a KOD-Plus-Ver.2 high-fidelity DNA polymerase kit (Toyobo Biotechnology Co., Ltd.) as described previously with minor modifications [31, 32]. The amplified product was then analysed on a 1.2% agarose gel.

Vaccine coverage

We obtained the administrative data on rotavirus vaccinations from the Unit of Vaccines and Immunization Services (UVIS) for Mbita sub-county. The administrative data included the target population aged <1 year that was eligible for receiving rotavirus vaccinations; the monthly targets for rotavirus vaccinations; and the monthly doses (1 and 2) of the rotavirus vaccine that were routinely administered to the target population in the sub-county. Using these data, we estimated the percentage of rotavirus immunisation coverage in Mbita sub-county between August 2014 and July 2016. Coverage, defined as the proportion of vaccinated individuals among the target population, was calculated by dividing the number of individuals vaccinated with rotavirus vaccine dose 1 or 2 (numerator) by the number of individuals targeted for vaccination (denominator) within the same period (month/year). This proportion was then multiplied by 100 to obtain the percentage of coverage [33]. The vaccine coverage rates were calculated using OpenEpi Version 3.01, an online version of EPI Info version 3.5.3.2 (USD, Inc., Stone Mountain, GA, USA), at 95% confidence intervals by Fisher Exact (Clopper–Pearson) method.

Data analysis

Prevalence, age, and seasonal distribution of rotavirus gastroenteritis before and after the vaccine had been introduced were calculated using EPI Info version 3.5.3.2 (USD, Inc., Stone Mountain, GA, USA). We analysed AGE hospitalisations due to rotavirus before and after the vaccine had been introduced and calculated the percentage decline in the overall prevalence in rotavirus AGE and among the vaccine-eligible age category of children. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS for IBM-PC, release 18.0; SPSS Inc., Chicago, IL, USA). Differences in proportions were tested using the chi-squared ($\chi 2$) test. A *P*-value of <0.05 was considered to be significant.

Results

Vaccine coverage

The overall rotavirus immunisation coverage in Mbita sub-county for dose 1 and 2 for the period between August 2014 and July 2016 was estimated at 74% (95% CI: 73–75%) and 62% (95% CI: 61–63%), respectively. The vaccine coverage increased for both dose 1 and 2 over the study period. The coverage for dose 1 increased from 66% (95% CI: 65–67%) in the first year of vaccine introduction to 81% (95% CI: 80–82%) in the second year. Similarly, the rate of coverage for dose 2 rose to 72% (95% CI: 71–74%) in the second year of vaccine introduction from 51% (95% CI: 50–52%) in the first year (Table 1).

Rotavirus-associated hospitalisations

From August 2011 through July 2016, 605 children <5 years of age with AGE were enrolled in the study and had their stools tested for RVA by ELISA. In the pre-vaccine introduction period, 12.2% (47/386; 95% CI: 9.2–15.7%) of the children tested positive for RVA. In the post-vaccine period, the RVA positivity rate was 6.4%

Table 1 Prevalence of rotavirus gastroenteritis before and after vaccine introduction in Kenya

	Rotavirus season	Gastroenteritis cases tested	Rotavirus positive	% Positive (95% CI)	Overall Prevalence	Vaccine coverage
Pre-vaccine	Aug 2011–Jul 2012	200	26	13 (9–18)	47/386	
	Aug 2012–Jul 2013	100	8	8 (4–15)	12% (9–16)	
	Aug 2013–Jul 2014	86	13	15 (9–24)		
Post-vaccine	Aug 2014–Jul 2015	96	7	7 (3–14)	14/219	51%
	Aug 2015–Jul 2016	123	7	6 (3–11)	6% (4–10)	72%
Total		605	61	10 (8–13)		62%

CI, confidence interval; Aug, August; Jul, July. Pre-vaccine refers to the period from August 2011 to July 2014, and Post-vaccine refers to the period from August 2014 to July 2016. Vaccine coverage is for dose 2.

(14/219; 95% CI: 3.7–10.3%), indicating an overall reduction of 47.5% (95% CI: 27.1–64.3%) (Table 1). The rate of reduction in RVA-associated hospitalisations increased from 40.2% (95% CI: 20.7–56.5%) in the first year of vaccine introduction to 53.3% (95% CI: 34.2–71.5%) in the second year.

Before the vaccine was introduced, RVA was detected most frequently (51%) in children aged <12 months (vaccine-eligible group) with an early peak at 6–11 months. After vaccine introduction, the proportion of RVA cases in children <12 months of age decreased to 14%, with the most detections (57%) among children aged 12–23 months. Reductions in RVA positivity were observed across all age groups but, overall, were most pronounced among the vaccine-eligible group (Figure 1).

The monthly counts of RVA hospitalisations among children <5 years of age substantially decreased in the post-vaccine period. Seasonal peaks of RVA hospitalisations also were substantially reduced after vaccine introduction (Figure 2).

Distribution of rotavirus G-P genotypes

Thirteen combinations of G and P genotypes were detected during the entire surveillance period. Of these, G1P[8] was the most common genotype (26%), followed by G2P[4] (20%) and G8P[4] (18%). Comparing the distribution of strains before and after vaccine introduction, the frequency of G1P[8], which was the most dominant strain alongside G8P[4] in the pre-vaccine period (18%), declined markedly in the post-vaccine period (5%). There was a substantial increase in the detection of G2P[4] (13%) after vaccine introduction and the strain replaced G1P[8] as the most frequently detected genotype during this period. G8P[4], which had predominated during the pre-vaccine period, was not detected in the post-vaccine period (Table 2).

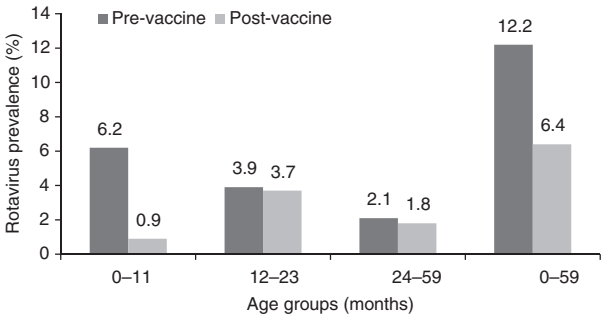

Figure 1 Age distribution of rotavirus-related acute gastroenteritis among children aged <5 years admitted for acute gastroenteritis at Mbita Sub-county Hospital, Western Kenya, in pre-vaccine (August 2011–July 2014) and post-vaccine (August 2014–July 2016) periods of study.

Discussion

The introduction of a monovalent rotavirus vaccine (RV1) into the Kenyan national immunisation programme was temporally associated with a 48% decrease in overall hospitalisations for rotavirus-associated gastroenteritis in children aged <5 years in a rural, resource-limited setting of Mbita, Western Kenya. The reductions were consistent with an increase in the coverage of the rotavirus vaccine in Kenya [34] and in the study setting as well [35]. A 40% decline in hospitalisations for rotavirus gastroenteritis was observed in the first post-vaccination year, with vaccine coverages of 66% and 51% for dose 1 and 2, respectively. As the coverage increased to 81% for dose 1 and 72% for dose 2 at the end of the second year of vaccine introduction, concurrent reductions of 53% in rotavirus hospitalisations were observed. The observed reductions in rotavirus-specific gastroenteritis are consistent with observations in low-income countries of Africa and middle-income countries in the Americas. Early adopters of the vaccine in Africa

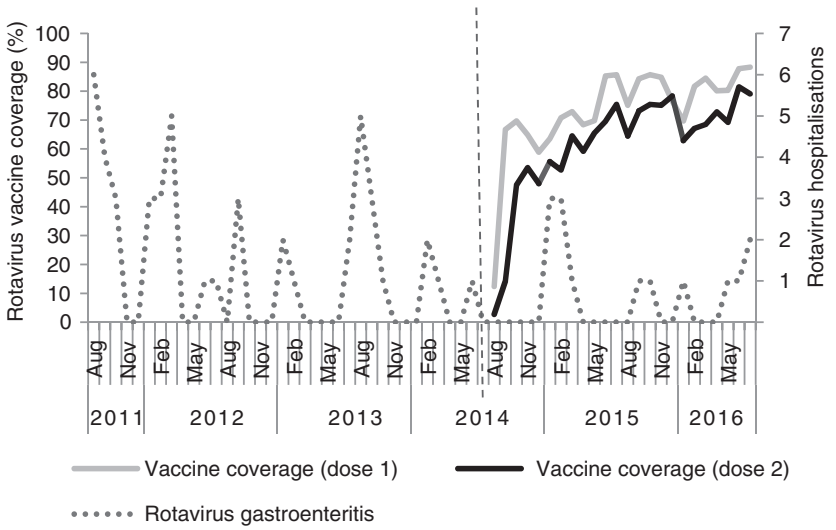

Figure 2 Trends in hospital admissions for rotavirus-related acute gastroenteritis among children aged <5 years at Mbita Sub-county Hospital, Western Kenya, before (August 2011–July 2014) and after (August 2014–July 2016) rotavirus vaccine introduction. Vaccine was introduced nationally and in the study community in July 2014 (dashed line).

Table 2 Distribution of rotavirus G-P genotypes in Kenya before and after vaccine introduction

Strain	Pre-vaccine cases (%)	Post-vaccine cases (%)	Total cases (%)
G1P[8]	11 (18)	5 (8)	16 (26)
G2P[4]	4 (7)	8 (13)	12 (20)
G4P[8]	1 (2)	0 (0)	1 (2)
G1P[4]	3 (5)	0 (0)	3 (5)
G2P[6]	1 (2)	1 (2)	2 (3)
G3P[6]	3 (5)	0 (0)	3 (5)
G4P[6]	3 (5)	0 (0)	3 (5)
G8P[4]	11 (18)	0 (0)	11 (18)
G8P[6]	3 (5)	0 (0)	3 (5)
G8P[8]	4 (7)	0 (0)	4 (7)
G12P[6]	1 (2)	0 (0)	1 (2)
G1G8P[8]	1 (2)	0 (0)	1 (2)
GNTP[6]	1 (2)	0 (0)	1 (2)
Total	47	14	61

Pre-vaccine refers to the period from August 2011 to July 2014. Post-vaccine refers to the period from August 2014 to July 2016. GNT refers to those strains whose G genotype could not be detected using the existing primer sets.

reported a 24–49% decline in rotavirus hospitalisations among children aged <5 years within 2 years of its introduction [18–22]. In several middle-income countries in the Americas, declines in rotavirus-associated gastroenteritis hospitalisations have been reported to range between 49% and 89% after the introduction of rotavirus vaccination [7–9].

During the pre-vaccine era, cases of rotavirus gastroenteritis reached an early peak at 6–11 months of age among our study population, with 51% of the children hospitalised for rotavirus gastroenteritis being <12 months of age. A similar phenomenon of rotavirus infecting infants early in life was previously reported in Kenya [36, 37]. After vaccine introduction, reductions in rotavirus positivity occurred in all age groups studied but were greatest in infants <12 months, who constitute the vaccine-eligible population. These observations are consistent with reports from other African countries that were among the early adopters of the rotavirus vaccine, reporting greater initial declines in the proportion of rotavirus cases among younger age groups that receive vaccinations in the initial years of the vaccination [13–15, 18–20]. Thus, our data provide evidence for a major public health impact of rotavirus vaccination among the infants in view of the fact that gastroenteritis cases within this age bracket are generally more severe and pose a greater risk of morbidity and mortality.

There was a change in the seasonal pattern of rotavirus gastroenteritis after the vaccine was introduced. The pre-vaccine years were characterised by distinct seasonal peaks in rotavirus-associated hospitalisations among children aged <5 years, whereas after vaccine introduction, we observed less pronounced peaks in rotavirus hospitalisations, providing additional evidence that the declines can be attributed to the effect of rotavirus vaccinations. Similar observations of diminished peaks in hospitalisations from rotavirus gastroenteritis have been reported

elsewhere in Africa after introduction of the vaccine [14, 15, 19, 20].

A remarkable genotypic diversity of rotavirus strains, characterised by unusual, mixed, emerging, and temporal fluctuations of genotypes was observed in this study setting before and after the vaccine had been introduced. Although studies have shown that RV1 vaccine protects against a variety of rotavirus strains, conferring immunity to partly or fully heterotypic strains (i.e. strains that share either the G or the P type components of the vaccine strain, or share neither component, respectively) may be of concern in these poor settings where genotypic diversity is common [38]. Thus, it would be interesting to evaluate the effectiveness of the vaccine against the strains detected in this study setting. Nevertheless, the demonstrated protective effect of rotavirus vaccination reported in this study is quite encouraging, as it is in a population with a remarkable genotypic diversity of rotavirus strains.

There is no broad scientific consensus regarding the long-term effects of rotavirus vaccination on the strain distribution. Although changes in genotype distribution have been observed after mass vaccinations with RV1 and/or RV5 in many countries [21, 22, 39–44], the issue of whether these changes can be attributed to the actual vaccines remains unclear. After introduction of the vaccine in Kenya, we observed an upsurge in G2P[4] strains. However, it is noteworthy that temporal fluctuations in rotavirus genotypes have been detected in Kenya prior to the introduction of the vaccine [36, 45–48]. Further, the absence of data on the strain-specific effectiveness of RV1 in this setting and the limited post-vaccine observation period that did not permit monitoring for any sustained predominance of the G2P[4] strains limited our attempts to attribute the changing prevalence of these genotypes to vaccine-induced selective pressure.

An ecological study such as this has some limitations. First, the observed reduction in the cases of rotavirus gastroenteritis did not take into account seasonal trends in other causes of gastroenteritis or changes in hospital referral patterns, which may have impacted the extent of gastroenteritis hospitalisations. However, to our knowledge, there were no abrupt changes in hospital referral patterns in the study area. Second, the study did not evaluate rotavirus vaccination status of each individual child due to challenges with record keeping, which would permit an estimation of the effectiveness of the vaccine. Third, vaccine administrative data were used to estimate the rotavirus immunisation coverage in the study area. However, it is possible that these estimates could be biased due to inaccurate numerators or denominators, errors in recording vaccinations at health facilities, and errors in compiling data on vaccinations for reporting to higher levels [49]. Fourth, there was no untreated comparison group in this study. Although a valid comparison group for the evaluation of such a nationwide intervention is generally problematic, future studies are necessary to assess whether there was a dose–response by comparing the magnitude of change in the outcome of interest before and after vaccination between multiple counties with differing coverage levels.

Conclusions

The marked reductions in rotavirus gastroenteritis hospitalisations following the introduction of rotavirus vaccine and which were most pronounced among the vaccine-eligible children and commensurate with increasing vaccine coverage provide early evidence of the public health value of rotavirus vaccination in a resource-limited setting in Kenya. Thus, our data strongly support the continued use of the rotavirus vaccine in the Kenyan national immunisation programme. The findings support a call for extending coverage on the second dose of the vaccine beyond the current level of 72% to maximise the impact of the vaccine. Continued monitoring will be necessary to assess whether the observed changes in rotavirus disease epidemiology are sustained over the long term. Vaccine effectiveness studies should also be conducted to support evaluations of the impact of vaccinations on the distributions of various rotavirus strains due to possible vaccine-driven selection pressure.

Acknowledgements

We wish to thank the Director of the Kenya Medical Research Institute for his collaborative support. We are grateful to the Medical Superintendent, Mbita Sub-county Hospital, for facilitating the active surveillance of rotavirus gastroenteritis at the facility. We also acknowledge the support of the Head of Unit of Vaccines and Immunization Services, Mbita sub-county, for providing the sub-county's rotavirus vaccine administrative data. This study was supported, in part, by a Grant-in-Aid for Scientific Research, Japan (Research B: 15H05286) and the Program for Nurturing Global Leaders in Tropical and Emerging Communicable Diseases (TECD), Nagasaki University, Japan.

References

1. Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD; WHO-coordinated Global Rotavirus Surveillance Network. Global, regional, and national estimates of

rotavirus mortality in children 5 years of age, 2000–2013. *CID* 2016: **62**(Suppl 2): 96–105.
2. van Hoek AJ, Ngama M, Ismail A *et al.* A cost effectiveness and capacity analysis for the introduction of Universal Rotavirus Vaccination in Kenya: comparison between Rotarix and RotaTeq vaccines. *PLoS ONE* 2012: **7**: e47511.
3. Tate JE, Rheingans RD, O'Reilly CE *et al.* Rotavirus disease burden and impact and cost-effectiveness of a rotavirus vaccination program in Kenya. *J Infect Dis* 2009: **200**(Suppl): 76–84.
4. World Health Organization. Meeting of the immunization strategic advisory group of experts, April 2009-conclusions and recommendations. *Wkly Epidemiol Rec* 2009: **84**(23): 220–236.
5. Rota Council. Global Introduction Status, 2017. http://rotacouncil.org/vaccine-introduction/global-introduction-status/ [3 July 2017].
6. Kenya National Bureau of Statistics (KNBS); ICF Macro, 2015. Kenya Demographic and Health Survey 2014. Key Indicators 2014. https://dhsprogram.com/pubs/pdf/FR308/FR308.pdf [5 July 2017].
7. Richardson V, Hernandez-Pichardo J, Quintanar-Solares M, Esparza-Aguilar M, Johnson B, Gomez-Altamirano CM. Effect of rotavirus vaccination on death from childhood diarrhea in Mexico. *N Engl J Med* 2010: **362**(4): 299–305.
8. do Carmo GM, Yen C, Cortes J, Siqueira AA, de Oliveira WK, Cortez-Escalante JJ. Decline in diarrhea mortality and admissions after routine childhood rotavirus immunization in Brazil: a time-series analysis. *PLoS Med* 2011: **8**(4): e1001024.
9. Patel MM, Steele D, Gentsch JR, Wecker J, Glass RI, Parashar UD. Real-world impact of rotavirus vaccination. *Pediatr Infect Dis J* 2011: **30**(Suppl 1): 1–5.
10. Bayard V, DeAntonio R, Contreras R *et al.* Impact of rotavirus vaccination on childhood gastroenteritis-related mortality and hospital discharges in Panama. *Int J Infect Dis* 2012: **16**: e94–e98.
11. Gastanaduy PA, Curns AT, Parashar UD, Lopman BA. Gastroenteritis hospitalizations in older children and adults in the United States before and after implementation of infant rotavirus vaccination. *JAMA* 2013: **310**: 851–853.
12. Clarke MF, Davidson GP, Gold MS, Marshall HS. Direct and indirect impact on rotavirus positive and all-cause gastroenteritis hospitalisations in South Australian children following the introduction of rotavirus vaccination. *Vaccine* 2011: **29**: 4663–4667.
13. Parashar UD, Johnson H, Steele AD, Tate JE. Health impact of rotavirus vaccination in developing countries: progress and way forward. *CID* 2016: **62**(Suppl 2): 91–95.
14. Enane LA, Gastañaduy PA, Goldfarb DM *et al.* Impact of rotavirus vaccination on hospitalizations and deaths from childhood gastroenteritis in Botswana. *Clin Infect Dis* 2016: **62**(suppl 2): S168–S174.
15. Groome MJ, Zell ER, Solomon F *et al.* Temporal association of rotavirus vaccine introduction and reduction in all-cause childhood diarrheal hospitalizations in South Africa. *Clin Infect Dis* 2016: **62**(suppl 2): S188–S195.
16. Groome MJ, Page N, Cortese MM *et al.* Effectiveness of monovalent human rotavirus vaccine against admission to hospital for acute rotavirus diarrhoea in South African children: a case-control study. *Lancet Infect Dis* 2014: **14**: 1096–1104.
17. Tsolenyanu E, Mwenda JM, Dagnra A *et al.* Early evidence of impact of monovalent rotavirus vaccine in Togo. *Clin Infect Dis* 2016: **62**(Suppl 2): S196–S199.
18. Mpabalwani EM, Simwaka CJ, Mwenda JM *et al.* Impact of rotavirus vaccination on diarrheal hospitalizations in children aged <5 years in Lusaka, Zambia. *Clin Infect Dis* 2016: **62**(suppl 2): S183–S187.
19. Bar-Zeev N, Jere KC, Bennett A *et al.* Population impact and effectiveness of monovalent rotavirus vaccination in urban Malawian children 3 years after vaccine introduction: ecological and case-control analyses. *Clin Infect Dis* 2016: **62**(suppl 2): S213–S219.
20. Ngabo F, Tate JE, Gatera M *et al.* Effect of pentavalent rotavirus vaccine introduction on hospital admissions for diarrhoea and rotavirus in children in Rwanda: a time-series analysis. *Lancet Glob Health* 2016: **4**: e129–e136.
21. Msimang VM, Page N, Groome MJ *et al.* Impact of rotavirus vaccine on childhood diarrheal hospitalization after introduction into the South African public immunization program. *Pediatr Infect Dis J* 2013: **32**: 1359–1364.
22. Armah G, Pringle K, Enweronu-Laryea CC *et al.* Impact and effectiveness of monovalent rotavirus vaccine against severe rotavirus diarrhea in Ghana. *Clin Infect Dis* 2016: **62** (suppl 2): S200–S207.
23. Bar-Zeev N, Kapanda L, Tate JE *et al.* Effectiveness of a monovalent rotavirus vaccine in infants in Malawi after programmatic roll-out: an observational and case-control study. *Lancet Infect Dis* 2015: **15**: 422–428.
24. Tate JE, Ngabo F, Donnen P *et al.* Effectiveness of pentavalent rotavirus vaccine under conditions of routine use in Rwanda. *Clin Infect Dis* 2016: **62**(suppl 2): S208–S212.
25. Sigei C, Odaga J, Mvundura M, Madrid Y, Clark AD. Cost-effectiveness of rotavirus vaccination in Kenya and Uganda. *Vaccine* 2015: **33**(Suppl 1): A109–A118.
26. Nelson EAS, Glass RI. Rotavirus: realising the potential of a promising vaccine. *Lancet* 2010: **376**: 568–570.
27. Bundervoet T, Maiyo L, Sanghi A. Bright Lights, Big Cities: Measuring National and Subnational Economic Growth in Africa from Outer Space, with an Application to Kenya and Rwanda. The World Bank, Kenya and Rwanda Country Management Unit, Macroeconomics and Fiscal Management Global Practice Group, and Poverty Global Practice Group, 2015. http://econ.worldbank.org. [7 April 2017].
28. Wanyua S, Ndemwa M, Kensuke G *et al.* Profile: the Mbita health and demographic surveillance system. *Int J Epidemiol* 2013: **42**: 1678–1685.
29. World Health Organization. Generic protocols for hospital-based surveillance to estimate the burden of rotavirus gastroenteritis in children and a community-based survey on utilization of health care services for gastroenteritis in

children. Field test version. WHO/V&B/02.15. www.who.int/vaccines-documents/ [25 June 2017].
30. Taniguchi K, Urasawa T, Morita Y, Greenberg HB, Urasawa S. Direct serotyping of human rotavirus in stools by an enzyme-linked immunosorbent assay using serotype 1-, 2-, 3-, and 4-specific monoclonal antibodies to VP7. *J Infect Dis* 1987: **155**: 1159–1166.
31. Taniguchi K, Wakasugi F, Pongsuwanna Y *et al.* Identification of human and bovine rotavirus serotypes by polymerase chain reaction. *Epidemiol Infect* 1992: **109**: 303–312.
32. Taniguchi K, Urasawa T, Kobayashi N, Gorziglia M, Urasawa S. Nucleotide sequence of VP4 and VP7 genes of human rotaviruses with subgroup I specificity and long RNA pattern: implication for new G serotype specificity. *J Virol* 1990: **64**: 5640–5644.
33. Republic of Kenya, Ministry of Health. Immunization Manual for Health Workers. http://www.mchip.net/sites/default/files/mchipfiles/Immunization%20Manual%20for%20Health%20Workers_updated.pdf [10 July 2017].
34. The WHO and UNICEF. *Estimates of National Immunization Coverage*. The WHO and UNICEF: Kenya, 2015. www.who.int/immunization/monitoring_surveillance/data/ken.pdf [11 July 2017].
35. Wandera EA, Mohammad S, Ouko J, Yatitch J, Taniguchi K, Ichinose Y. Variation in rotavirus vaccine coverage by sub-counties in Kenya. *Trop Med Health* 2017: **45**: 9.
36. Wandera EA, Mohammad S, Komoto S *et al.* Molecular epidemiology of rotavirus gastroenteritis in Central Kenya before vaccine introduction, 2009-2014. *J Med Virol* 2017: **89**: 809–817.
37. Nokes DJ, Abwao J, Pamba A *et al.* Incidence and clinical characteristics of group a rotavirus infections among children admitted to hospital in Kilifi. *Kenya. PLoS Med* 2008: **5**: e153.
38. Leshem E, Lopman B, Glass R *et al.* Distribution of rotavirus strains and strain-specific effectiveness of the rotavirus vaccine after its introduction: a systematic review and meta-analysis. *Lancet Infect Dis* 2014: **4**: 847–856.
39. Carvalho-Costa FA, Volotão Ede M, de Assis RM *et al.* Laboratory-based rotavirus surveillance during the introduction of a vaccination program, Brazil, 2005-2009. *Pediatr Infect Dis J* 2011: **30**: S35–S41.
40. Hull JJ, Teel EN, Kerin TK *et al.* United States rotavirus strain surveillance from 2005 to 2008: genotype prevalence before and after vaccine introduction. *Pediatr Infect Dis J* 2011: **30**: S42–S47.
41. Kirkwood CD, Boniface K, Barnes GL, Bishop RF. Distribution of rotavirus genotypes after introduction of rotavirus vaccines, Rotarix and RotaTeq, into the National Immunization Program of Australia. *Pediatr Infect Dis J* 2011: **30**: S48–S53.
42. Zeller M, Rahman M, Heylen E *et al.* Rotavirus incidence and genotype distribution before and after national rotavirus vaccine introduction in Belgium. *Vaccine* 2010: **28**: 7507–7513.
43. Matthijnssens J, Zeller M, Heylen E *et al.* Higher proportion of G2P[4] rotaviruses in vaccinated hospitalized cases compared with unvaccinated hospitalized cases, despite high vaccine effectiveness against heterotypic G2P[4] rotaviruses. *Clin Microbiol Infect* 2014: **20**: 702–710.
44. Pitzer VE, Bilcke J, Heylen E *et al.* Did large-scale vaccination drive changes in the circulating rotavirus population in Belgium? *Sci Rep* 2015: **5**: 18585.
45. Kiulia NM, Kamenwa R, Irimu G *et al.* The epidemiology of human rotavirus associated with diarrhoea in Kenyan children: a review. *J Trop Pediatr* 2008: **54**: 401–405.
46. Kiulia NM, Nyaga MM, Seheri ML *et al.* Rotavirus G and P types circulating in the eastern region of Kenya: predominance of G9 and emergence of G12 genotypes. *Pediatr Infect Dis J* 2014: **33**: S85–S88.
47. Nokes DJ, Peenze I, Netshifhefhe L *et al.* Rotavirus genetic diversity, disease association and temporal change in hospitalized rural Kenyan children. *J Infect Dis* 2010: **202**: S180–S186.
48. Nyangao J, Page N, Esona M *et al.* Characterization of human rotavirus strains from children with diarrhea in Nairobi and Kisumu, Kenya, between 2000 and 2002. *J Infect Dis* 2010: **202**: S187–S192.
49. Murray CJL, Shengelia B, Gupta N, Moussavi S, Tandon A, Thieren M. Validity of reported vaccination coverage in 45 countries. *Lancet* 2003: **362**: 1022–1027.

Corresponding Author **Ernest Apondi Wandera**, KEMRI/Nagasaki University, Institute of Tropical Medicine, Kenya Research Station, PO Box 19993-00202, Nairobi, Kenya. Tel.: +254-20-272-5120; Fax +254-20-272-5144; E-mail wandesh2000@yahoo.com