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# Impact of rotavirus vaccination on rotavirus and all-cause gastroenteritis in peri-urban Kenyan children

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ABSTRACT

A monovalent rotavirus vaccine (RV1) was introduced into the National Immunization Program in Kenya in July 2014. We examined the impact of the vaccine on hospitalization for all-cause acute gastroenteritis (AGE) and rotavirus-specific AGE and strain distribution at a large referral hospital which serves a predominantly peri-urban population in Central Kenya. Data on rotavirus AGE and strain distribution were derived from ongoing hospital-based AGE surveillance. Hospital administrative data were used to compare trends in all-cause AGE. Pre-vaccine (July 2009–June 2014) and post-vaccine (July 2014–June 2016) periods were compared for changes in hospitalization for all-cause AGE and rotavirus AGE and strain distribution. Following the vaccine introduction, the proportion of children aged <5 years hospitalized for rotavirus declined by 30% (95% CI: 19–45%) in the first year and 64% (95% CI: 49–77%) in the second year. Reductions in rotavirus positivity were most pronounced among the vaccine-eligible group (<12 months) in the first year post-vaccination at 42% (95% CI: 28–56%). Greater reductions of 67% (95% CI: 51–79%) were seen in the second year in the 12–23 months age group. Similarly, hospitalizations for all-cause AGE among children <5 years of age decreased by 31% (95% CI: 24–40%) in the first year and 58% (95% CI: 49–67%) in the second year of vaccine introduction. Seasonal peaks of rotavirus and all-cause AGE were reduced substantially. There was an increased detection of G2P[4], G3P[6] and G3P[8], which coincided temporally with the timing of the vaccine introduction. Thus, introducing the rotavirus vaccine into the routine immunization program in Kenya has resulted in a notable decline in rotavirus and all-cause AGE hospitalizations in Central Kenya. This provides early evidence for public health policy makers in Kenya to support the sustained use of the rotavirus vaccine in routine immunizations.



## 1. Introduction

Group A rotavirus (RVA) is the leading cause of severe acute gastroenteritis (AGE) among children <5 years of age globally and is estimated to cause 215,000 deaths annually [1]. The majority of these deaths occur in low-income countries, particularly in sub-Saharan Africa, due to a lack of timely and appropriate treatment for dehydration [2]. In Kenya, prior to the introduction of rotavirus vaccine, RVA caused more than 3908 deaths [1], 3015 outpatient visits and 279 hospitalizations per 100,000 children <5 years annually [3], with an annual cost to the healthcare system of US$10.8 million [4]. In Central Kenya, we reported a 27.5% prevalence rate of RVA gastroenteritis in our five-year pre-vaccine hospital-based surveillance [5].

Safe and effective rotavirus vaccines are considered to be important tools for reducing the burden of AGE, thereby, contributing to the achievement of the Sustainable Development Goal 3 [6,7]. In 2009, two rotavirus vaccines: RotaTeq® (Merck & Co. Inc., USA), a pentavalent rotavirus vaccine (RV5) composed of five

*Abbreviations:* RVI, Monovalent Rotavirus Vaccine; RV5, Pentavalent Rotavirus Vaccine; AGE, Acute Gastroenteritis; RVA, Group A rotavirus; GAVI, Global Alliance for Vaccines Initiative; EPI, Expanded Program on Immunization; DALY, Disability-Adjusted Life-Year; KCH, Kiambu County Hospital; VE, Vaccine Effectiveness.

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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 by the World Health Organization (WHO) for global use [8]. Whereas clinical trials of these vaccines demonstrated a high efficacy against severe rotavirus gastroenteritis in high- and middle-income countries in the Americas and Europe (85%–98%) [9,10], trials in low- and middle-income countries in Africa and Asia demonstrated a lower efficacy (40–70%) [11–13]. Nonetheless, the benefits of vaccination could still be substantial in these countries even with a lower efficacy, given the high baseline burden of severe rotavirus disease in these settings.

As of May 1, 2016, rotavirus vaccinations had been implemented in the national immunization programs of 81 countries, including 38 low-income countries being supported by the GAVI Alliance [14]. Impressive declines in rotavirus and all-cause AGE hospitalizations and deaths have been observed in many high and middle-income countries in the Americas and Europe following the introduction of rotavirus vaccinations [15–18]. In some of these countries, rotavirus vaccination has also resulted in declines in rotavirus disease among children who were not vaccine eligible, a phenomenon referred to as herd immunity [19,20]. Similarly, there is increasing evidence to suggest that rotavirus vaccines will have a significant impact on infant morbidity and mortality in developing countries in Africa [21–30].

In July 2014, Kenya introduced the two-dose RV1 into her Expanded Program on Immunization (EPI) through co-financing with the GAVI Alliance. The vaccine is administered orally at 6 and 10 weeks of age and is aimed at protecting over 1.5 million children in the country from severe diarrhea. Cumulated over the first five years of life, rotavirus vaccinations are predicted to prevent 34% of outpatient visits, 31% of hospitalizations and 42% of deaths in Kenya [3]. It is further estimated that between the years 2014 and 2033, rotavirus vaccinations will avert 60,935 undiscounted deaths and 216,454 hospital admissions in Kenya's under-fives. Over the next 20-year period, the government health service is predicted to avoid costs amounting to US$ 30 million. In addition, the cost per disability-adjusted life-year (DALY) averted from a government perspective is estimated to be US$ 38 million [31].

The nationwide rollout of rotavirus vaccinations in Kenya has offered an opportunity to assess the real-world impact of the vaccine in preventing and reducing the health burden of severe childhood diarrhea in the country. In this regard, we conducted a hospital-based surveillance in Central Kenya between July 2009 and June 2014 to provide baseline data for monitoring the impact of the vaccine [5]. In this study, we report on the impact of rotavirus vaccinations on all-cause AGE and rotavirus-specific AGE and strain distribution in Central Kenya two years after the vaccine was introduced into the country's EPI.

## 2. Materials and methods

### 2.1. Study setting

From July 2009 to June 2016, we conducted an active hospital-based surveillance for rotavirus gastroenteritis in pediatric wards of Kiambu County Hospital (KCH). The five-year period (July 2009–June 2014) was defined as the pre-vaccine period, while the two-year period (July 2014–June 2016) was defined as the post-vaccine period. KCH is the main referral hospital in Kiambu County in the Central region of Kenya. Kiambu is a peri-urban county. The 2009 Population and Housing Census indicate that the county had a population of 1,623,282 in 2009 and the population was projected to reach 2,032,466 by the end of 2017 [32]. The county's population aged <5 years was estimated at 231,372 in 2015 whereas that aged <1 year being targeted for rotavirus vaccination was 47,412 in the same year [32]. According to the county's Unit of Vaccines and Immunization Services, rotavirus vaccine was universally rolled out in the county at the beginning of July 2014. The vaccine achieved a rapid increase in coverage from the onset, with dose 2 recording 82% coverage in 2014 and over 100% in 2016 [33].

The study subjects were children <5 years of age who were hospitalized at KCH with severe AGE and having experienced an episode of 3 looser than normal or watery stools in a 24-h period for not more than 7 days with or without episodes of vomiting [34]. Rotavirus infections cause acute gastroenteritis and the symptoms generally resolve in 3–7 days [34]. The children either came directly from the community or were referred from peripheral community health centers and dispensaries. Decisions regarding hospitalization, investigations and treatment were at the discretion of the attending clinicians.

### 2.2. Ethical consideration

This study was approved by the Kenya Medical Research Institute/National Ethical Review Committee (SSC No. 1323). Informed written consent was sought from the parents or guardians of all the participating children.

### 2.3. Sample collection

Demographic and clinical data were collected from the children who met all the inclusion criteria using a pathological investigation form adapted from the WHO generic protocol for rotavirus surveillance [34]. After obtaining written parental informed consent, fecal samples were collected in clean sterile containers within 48 h of admission. Each sample was labeled according to the date of collection and the sample number. The samples were kept 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 they were processed.

### 2.4. RVA detection

About 1 ml of a 10% fecal suspension was prepared for 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 followed by centrifugation at 10,000 rpm for 5 min. The supernatant was transferred to a new tube and stored at −30 °C until used. Specimens from the 10% fecal suspension were tested for RVA antigen by ELISA, as described previously [35]. All specimens were stored at −80 °C for further testing.

### 2.5. G And P genotyping

RVA double-stranded RNA was extracted from 10% fecal suspensions with ISOGEN-LS (Nippon Gene Co., Ltd., Toyama, Japan) according to the manufacturer's protocol. The RNA was reverse transcribed into the complementary DNA (cDNA) using a ReverTra Ace® qPCR RT Kit (Toyobo Biotechnology Co., Ltd., Japan). The cDNA was then amplified in a two-step multiplexed semi-nested 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 [36,37]. The amplified product was then analyzed on a 1.2% agarose gel.