

Impact of the introduction of rotavirus vaccine on hospital admissions for diarrhoea among children in Kenya: A controlled interrupted time series analysis

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Summary:

Following the national introduction of the rotavirus vaccine in Kenya, our impact evaluation across two surveillance sites indicates a substantial reduction in childhood hospitalisation due to rotavirus-associated and all-cause severe diarrhoea.

ABSTRACT

Introduction: Monovalent rotavirus vaccine, Rotarix™, was introduced in Kenya in July 2014, is recommended to infants as oral doses at ages 6 and 10 weeks. A multi-site study was established in two population based surveillance sites to evaluate vaccine impact on the incidence of rotavirus-associated hospitalisations (RVH).

Methods: Hospital-based surveillance was conducted from January 2010 to June 2017 for acute diarrhoea hospitalisations among children aged <5 years in two health facilities in Kenya. A controlled interrupted time series analysis was undertaken to compare RVH pre and post vaccine introduction using rotavirus negative cases as a control series. The change in incidence post vaccine introduction was estimated from a negative binomial model that adjusted for secular trend, seasonality and multiple health worker industrial actions (strikes).

Results: Between January 2010 and June 2017 there were 1513 and 1652 diarrhoea hospitalisations in Kilifi and Siaya; among those tested for rotavirus, 28% (315/1142) and 23% (197/877) were positive, respectively. There was a 57% (95% CI: 8 to 80) reduction in RVH observed in the first year post vaccine introduction in Kilifi and a 59% (95% CI: 20 to 79) reduction in Siaya. In the second year, RVH decreased further at both sites, 80% (95% CI: 46 to 93) reduction in Kilifi and 82% reduction in Siaya (95% CI: 61 to 92), and this reduction was sustained at both sites into the third year.

Conclusions: A substantial reduction of RVH and all-cause diarrhoea has been observed in two demographic surveillance sites in Kenya within 3 years of vaccine introduction.

Key words: Rotavirus vaccine, Interrupted time series, Control, Vaccine Impact

Introduction

Rotavirus is a major contributor to severe diarrhoea illness and related mortality, especially in low and middle income countries[1–3]. Global estimates suggest that in 2013, rotavirus accounted for 215000 or 3.4% of all deaths in children aged <5 years[4]. In 2009, the World Health Organisation (WHO) recommended that all countries, especially those with high diarrhoea associated child mortality rates, implement rotavirus immunisation programmes[5]. Kenya adopted this recommendation in July 2014[6,7]. Since then, two doses of live attenuated rotavirus vaccine (Rotarix™), in addition to oral polio, pneumococcal conjugate (PCV) and pentavalent vaccines, have been recommended to children in Kenya, targeted at 6 and 10 weeks of life, as part of the routine child immunisation programme[8,9]. It was estimated that introduction of this vaccine in Kenya would avert over 60,000 deaths and over 200,000 hospitalisations among children aged <5 years during the first 20 years of introduction[10]. Following vaccine introduction, we used demographic and hospital data from two population-based surveillance sites in Kenya to estimate the impact of the programme on rotavirus hospitalizations in children <5 years.

Methods

Geographical Location

The study was conducted in two regions with established demographic surveillance systems (DSS): the Kilifi Health and Demographic Surveillance System[11] (Kilifi HDSS), which is located on the Kenyan coast, and the Kenya Medical Research Institute (KEMRI) and the Centers for Disease Control and Prevention (CDC) Health and Demographic Surveillance System (Siaya HDSS) [12] in rural western Kenya near Lake Victoria. Hospitalisation, diarrhoea and rotavirus counts for children under 5 years of age were obtained from two government hospitals: Kilifi County Hospital located in the Kilifi HDSS and Siaya County Referral Hospital located in the Siaya HDSS.

Vaccine introduction and coverage

Rotavirus vaccine was introduced into the childhood vaccination programme in both Kilifi and Siaya counties in July 2014. Children who were aged 6 weeks or younger or born after the start of the rotavirus immunisation programme were eligible to receive one dose at 6 weeks and one dose at 10 weeks, though vaccine stock outs in November and December 2014 kept some eligible children from receiving vaccine. There was no catch-up campaign in either Kilifi or Siaya.

In Kilifi HDSS, vaccinations have been recorded comprehensively since 2008 through a network of approximately 30 health facilities (both private and public) (Supplementary Figure1), as part of the Kilifi vaccine monitoring study (KiVMS)[13]. In Siaya HDSS over 20 health facilities administer vaccines to children (Supplementary Figure2); since 2007, immunisation data have been collected for children aged <5 years during household data collection rounds, which occur 2-3 times per year[12]. In addition, the vaccination status of children enrolled in the rotavirus surveillance at Siaya County Referral Hospital is recorded at the time of hospital admission. In both sites, card confirmed vaccine information was captured by the field staff

Rotavirus surveillance

In 2009, to prepare for vaccine introduction[12,14], rotavirus surveillance was intensified at Siaya County Referral Hospital among children aged < 5 years who presented with three or more loose stools within a 24-hour period and one or more vomiting episodes. In Kilifi, rotavirus surveillance was initiated in late 2009 in inpatient children aged less than 13 years with three or more loose stools within a 24-hour period. Parents of eligible children were briefed on the potential risks and benefits before of the study before being asked to give consent by the study team. Stool samples were collected from eligible children, whose parents provided voluntary

informed consent, and tested for rotavirus antigen by Enzyme-Linked Immunosorbent Assay (ELISA), as described previously[14,15].

Surveillance was interrupted by 12 industrial actions (strikes), including 7 before and 5 after rotavirus vaccine introduction, by different cadres of health care workers as indicated in supplementary Table1.

Statistical analysis

We used a controlled interrupted time series analysis in which rotavirus negative diarrhoea hospitalisations acted as the control series to compare monthly RVH before and after rotavirus vaccine introduction in children <5 years of age. Specifically, RVH from the period 54 months prior (January 2010 to June 2014) were compared with hospitalisations from the period 36 months post (July 2014 to June 2017) vaccine introduction at each facility. For a month in which <100% of diarrhoea cases were tested for rotavirus, the number of rotavirus-positive cases was scaled by multiplying the total number of diarrhoea cases by the proportion rotavirus positive among those tested in that month.

A negative binomial regression was used to estimate the change in rotavirus hospitalisations in the first year (July 2014-June 2015), second year (July 2015-June 2016) and third year (July 2016-June 2017) post vaccine introduction. The model included rotavirus negative diarrhoea (the control series) as an offset, and calendar month and health worker industrial actions as covariates. Lag-1 Newey-West standard errors were used to adjust for autocorrelation[16]. A similar analysis was conducted for all cause diarrhoea using non-diarrhoea hospitalisations as the control series.

For the analysis of rotavirus positive diarrhea, a sensitivity analysis was conducted using a synthetic control[17-19] in the regression model instead of rotavirus negative cases. The synthetic control was generated by weighting three conditions (rotavirus

negative diarrhoea, pneumonia, malaria) – using SYNTH[20] command in Stata – so that their sum closely resembled the pre-vaccine rotavirus positive time series.

All statistical analyses were conducted using Stata13.1 software, (Stata Corporation, College Station, TX, USA). All datasets, Stata files and related documentation are available on an online data repository (<https://doi.org/10.7910/DVN/PH4COG>)[21].

Ethics Review

Ethical approval to conduct this study was granted by the KEMRI Scientific and Ethics Review Unit (SERU) (SSC # 3049) and the CDC's institutional review board (protocol #6968).

Results

Incidence and Seasonality

During the study period, there were 1513 and 1652 diarrhoea hospitalisations in Kilifi County Hospital and Siaya County Referral Hospital, respectively. In Kilifi, 1142 (75.5%) of the diarrhoea cases were tested and among those tested 315 (27.6%) were positive for rotavirus. In Siaya, 877 (53.1%) were tested and 197 (22.5%) were positive for rotavirus.

The proportion of children living in the study areas who received rotavirus vaccine increased with time. Between 2014 (year of introduction) and 2017, the proportion of aged <1 year with at least one dose increased from 31% to 73% in Kilifi and 16% to 75% in Siaya; the proportion fully vaccinated (two doses) in 2017 was 65% in Kilifi and 62% in Siaya. The highest coverage among infants was observed in 2016. Among children aged 12-23 months, the proportion with at least one dose increased from 0% to 86% in Kilifi and 0% to 94% in Siaya; coverage with two doses in 2017 was 84% and 92% respectively (Figure 1). The lowest proportions of vaccinated children were observed in 2014 across both sites due to vaccine roll-out in mid-year and the

unexpected stock-out. Among vaccinated children, the median age at receipt of the first dose was 6 weeks (interquartile range [IQR] 6 to 7) in Kilifi and 6 weeks (IQR: 6 to 7) in Siaya; median at age receipt of the second dose was 10 weeks (IQR 10 to 13) in Kilifi and 10 weeks (IQR 10 to 12) in Siaya.

Across the two demographic surveillance systems, overall diarrhoeal illness and rotavirus-specific illness displayed seasonal patterns which were dampened after the introduction of the vaccine (Figure 2). Siaya generally recorded higher diarrhoea and rotavirus associated diarrhoea incidences compared to Kilifi in the pre-vaccination era (Tables 1 and 2). In Kilifi, the highest numbers of rotavirus cases were recorded from April/May to September/November of the same year (Figure 2a). In Siaya, the RVH season began earlier in the year, usually in January /February (Figure 2b). At both sites, there was a declining trend in annual incidence of diarrhoea and RVH that began prior to the rotavirus immunization programme and continued following introduction of vaccine (2015-2017). During the years affected by industrial actions of health workers (Supplementary Table1) lower rotavirus incidence rates were recorded at both sites (Table 2).

Impact of vaccine using rotavirus negative control series

In Kilifi, we observed reduced rates of RVH among KHDSS resident children <5 years throughout the post vaccination period (Table 3 and Figure 3). When compared with rates from the pre-vaccine era, reductions were observed during the first year (57%, 95% CI: 8.0- 80.0), the second year (80%, 95% CI: 46-93) and third year (76%, 95% CI: 56-87) (Supplementary Figure 3(a)). Similarly, in Siaya there were reductions in the first year (59%, 95% CI: 20-79), second year (82%, 95% CI: 61-92) and third year (81%, 95% CI: 7-96) post vaccine introduction (Supplementary Figure 3(b)).

Impact of vaccine on all-cause diarrhoea

When examining trends in all-cause diarrhoea using non-diarrhoea hospitalizations as the control series, significant reductions were observed at both sites in post-vaccine introduction years (Table 3), though by a smaller magnitude compared to reductions in RVH. In Kilifi, impact of the vaccine on all-cause diarrhoea increased from 41% (95% CI: 16 to 59) in the first year to 48% (95% CI: 40 to 55) and 46% (95% CI: 34 to 55) in the second and third year respectively (Supplementary Figure 3(e)). In Siaya, there was a 41% (95% CI: 27 to 52) reduction of all cause diarrhoea in the first year followed by 60% (95% CI: 43 to 72) in the second year and 62% (95% CI: 38 to 77) reduction in the third year (Supplementary Figure 3(f)).

Impact of the vaccine on RVH using synthetic controls

The associated weights for each component of the synthetic control are shown in Supplementary Table 2, and the results of vaccine impact analysis in Supplementary Table 3 and Supplementary Figure 3. Vaccine impact estimates from this analysis are similar to those presented in Table 3, except that estimate for the last year in Kilifi was slightly lower than the corresponding estimate in Table 3. In Kilifi, impact of the vaccine was 67% (95% CI: 27 to 85) in the first year, 86% (95% CI: 64 to 94%) in the second year and 69% (95% CI: 45 to 83) in the third year. Similarly, in Siaya vaccine impact increased from 68% (95% CI: 33 to 84) in the first year to 89% (95% CI: 68 to 96) in the second year and 82% (95% CI: 8 to 96%) in the third year.

Discussion

We present results of an evaluation of the impact of rotavirus vaccine in Kenya using data from two population-based surveillance systems. Kenya introduced Rotarix™ vaccine into the national programme as a 2 dose schedule (6 and 10 weeks of age). We observed that most vaccinated children at both sites received either one or both doses of the vaccine within 3 weeks of the recommended time of vaccination. We estimate impact of the vaccine on RVH using non rotavirus hospitalisations and synthetic controls to control for any secular trends unrelated to the vaccine. Despite differences in the incidence of rotavirus disease in Kilifi and Siaya, as observed in this study and previous studies[15,22], the impact of vaccination was similar at both sites. In the first year post vaccine introduction, RVH declined by close to 60% in both Kilifi and Siaya, and all-cause diarrhoea declined by over 40% at both sites. In the second year of vaccination RVH further declined to over 80%, and this decline was sustained into the third post-vaccine introduction year with increasing coverage. Similarly, the positive impact of the vaccine on all-cause diarrhoea increased in the second and third years to as high as 60% reduction thus providing clear evidence of the substantial public health value of rotavirus immunization. These reductions suggest that vaccination of children aged less than two years, who are most likely to transmit rotavirus, optimizes direct and indirect protection against severe diarrhoeal infections.

Our estimates of rotavirus vaccine impact in the first year of vaccination are consistent with estimates from other African studies, which have ranged between 54% and 61% reduction for RVH and between 43% and 48% for all-cause diarrhoea hospitalizations[23,24]. The same studies reported increasing impact in the second year of vaccination as was observed in our study.

Using the average of the 2013's Kilifi and Siaya rotavirus disease incidence estimates (166 per 100,000 per year) to represent disease incidence in Kenya in the absence of

rotavirus vaccination, and assuming an under 5 population size of 6 million[25], an 80% vaccine impact equates to approximately 8,000 rotavirus-related hospitalisations prevented per year in Kenyan children <5 years. Over 20 years this corresponds to 160,000 hospitalisations prevented, which is similar to a previous estimate of 200,000[10].

Our study was impacted by health worker industrial actions and a pre-vaccine secular trend in RVH, possibly reflecting improved sanitation and hygiene[26]. To mitigate against these potential sources of bias we included the monthly rotavirus negative (or synthetic control) as an offset term in our regression model. Additionally, we excluded the longest strike period (July-December 2017) from our analysis. An important assumption of this analysis is that the rotavirus negative count reflects the counterfactual trend in rotavirus positive cases that would have been observed in the absence of vaccination. Another limitation we considered was that only a fraction (75% in Kilifi and 53% in siaya) of eligible diarrhoea cases were tested for rotavirus which represents another potential source of bias. To adjust for this, we imputed the number of rotavirus cases by multiplying the number of diarrhoea cases by the fraction that tested positive. This imputation assumes that the fraction rotavirus-positive is the same in those tested as it is in those who were not tested, and may itself introduce bias, particularly if the fraction tested changes over time.

In conclusion, results from this study suggest that the burden of rotavirus and all-cause diarrhoea declined substantially in Kenyan children in two regions of Kenya after rotavirus vaccine introduction. The estimates from this study represent total impact; indicating potential herd effects of the vaccine. Our estimates of vaccine impact on rotavirus and all-cause diarrhoea were consistent across the two study sites, and are consistent with findings from other African countries. These results contribute to the global estimates of rotavirus vaccine impact, especially in low and middle-income countries, and will likely inform future decisions by policy makers on rotavirus vaccination .

NOTES

Authors' Contributions:

Grievan P. Otieno: Formal analysis, Validation, Writing – original draft, Writing – review and editing, Data Curation. **Christian Bottomley:** Formal analysis, Validation, Writing – review and Editing. **Sammy Khagayi:** Validation, Investigation, Writing – review and editing. **Ifedayo Adetifa:** Validation, Investigation, Methodology, Writing – review and editing. **Mwanajuma Ngama:** Validation, Investigation, Writing – review and editing. **Richard Omore:** Validation, Investigation, Writing – review and editing. **Billy Ogwel:** Validation, Investigation, Writing – review and editing. **Betty E. Owor:** Validation, Investigation, Writing – review and editing. **Godfrey Bigogo:** Validation, Investigation, Writing – review and editing. **John B. Ochieng:** Validation, Investigation, Writing – review and editing. **Clayton Onyango:** Validation, Investigation, Writing – review and editing. **Jane Juma:** Validation, Investigation, Writing – review and editing. **Jason Mwenda:** Validation, Investigation, Writing – review and editing. **Tabu Collins:** Validation, Investigation, Writing – review and editing. **Jacqueline E. Tate:** Investigation, Methodology, Writing – review and editing. **Yaw Addo:** Investigation, Methodology, Writing – review and editing. **Tuck Britton:** Investigation, Methodology, Writing – review and editing. **Umesh D. Parashar:** Conceptualization, Investigation, Methodology, Writing – review and editing. **Robert F. Breiman:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review and editing. **Jennifer R. Verani:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review and editing. **D. James Nokes:** Funding acquisition, Methodology, Supervision (mentorship), Writing – review and editing

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Disclaimer

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Conflict of interest

Authors declare no conflict of interest.

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Figures Legends:

Figure 1: Proportion of children aged <5 years who received 2 doses of rotavirus vaccine between 2014 and 2017 in Kilifi and Siaya demographic surveillance sites.

Figure 2: Monthly counts of diarrhoea and rotavirus positive cases in Kilifi and Siaya from January 2010 to June 2017. Industrial actions by health workers are indicated by grey shading and the start of rotavirus vaccination in Kenya (July 2014) is indicated by an arrow.

Figure 3: Monthly counts of rotavirus positive cases (red line) and the counterfactual number of cases (dashed lines) predicted by the model assuming no vaccine introduction. The vertical line indicates the time of vaccine introduction in Kenya (July 2014).

TABLES

Table 1: Monthly diarrhoea and rotavirus counts and incidence rates per 100,000 children per year by site prior to rotavirus vaccine introduction (January 2010 - June 2014). Rotavirus incidence rates are scaled as described in methods.

| | Kilifi | | | | | | Siaya | | | | | |
|------------------|--------------|-----------|----------------------|--------------------|---------------------|---------------------|--------------|-----------|----------------------|--------------------|---------------------|---------------------|
| | Person Years | Diarrhoea | Rotavirus (Observed) | Rotavirus (scaled) | Diarrhoea Incidence | Rotavirus Incidence | Person Years | Diarrhoea | Rotavirus (Observed) | Rotavirus (Scaled) | Diarrhoea Incidence | Rotavirus Incidence |
| January | 20041 | 90 | 19 | 22 | 449 | 110 | 8169 | 218 | 22 | 49 | 2669 | 600 |
| February | 20041 | 86 | 12 | 16 | 429 | 80 | 8169 | 220 | 39 | 70 | 2693 | 857 |
| March | 20041 | 103 | 15 | 19 | 514 | 95 | 8169 | 136 | 25 | 51 | 1665 | 624 |
| April | 20041 | 113 | 21 | 29 | 564 | 145 | 8169 | 116 | 16 | 30 | 1420 | 367 |
| May | 20041 | 125 | 22 | 29 | 624 | 145 | 8169 | 160 | 24 | 37 | 1959 | 453 |
| June | 20041 | 158 | 37 | 47 | 788 | 235 | 8169 | 164 | 9 | 18 | 2008 | 220 |
| July | 16055 | 118 | 38 | 52 | 735 | 324 | 6769 | 111 | 8 | 13 | 1640 | 192 |
| August | 16055 | 78 | 39 | 46 | 486 | 287 | 6769 | 73 | 8 | 13 | 1078 | 192 |
| September | 16055 | 65 | 25 | 33 | 405 | 206 | 6769 | 65 | 9 | 12 | 960 | 177 |
| October | 16055 | 58 | 12 | 14 | 361 | 87 | 6769 | 70 | 7 | 11 | 1034 | 163 |
| November | 16055 | 68 | 5 | 6 | 424 | 37 | 6769 | 73 | 6 | 12 | 1078 | 177 |
| December | 16055 | 40 | 4 | 6 | 249 | 37 | 6769 | 81 | 9 | 19 | 1197 | 281 |

Table 2: Annual diarrhoea and rotavirus incidence rates per 100,000 children under 5 years in Kilifi and Siaya, Kenya.

| Year | Kilifi | | | | | | Siaya | | | | | |
|------|---------------------|-----------|----------------------|---------------------|---------------------|---------------------|---------------------|-----------|----------------------|---------------------|---------------------|---------------------|
| | Population Estimate | Diarrhoea | Rotavirus (Observed) | Rotavirus (scaled)* | Diarrhoea Incidence | Rotavirus Incidence | Population Estimate | Diarrhoea | Rotavirus (Observed) | Rotavirus (scaled)* | Diarrhoea Incidence | Rotavirus Incidence |
| 2010 | 47746 | 319 | 70 | 93 | 668 | 195 | 21885 | 500 | 78 | 124 | 2285 | 567 |
| 2011 | 48083 | 323 | 74 | 90 | 672 | 187 | 20953 | 446 | 53 | 107 | 2129 | 511 |
| 2012 | 48412 | 213 | 56 | 70 | 440 | 145 | 19947 | 201 | 26 | 50 | 1008 | 251 |
| 2013 | 48414 | 140 | 31 | 42 | 289 | 87 | 18439 | 218 | 21 | 45 | 1182 | 244 |
| 2014 | 47835 | 196 | 31 | 40 | 410 | 84 | 16803 | 162 | 7 | 13 | 964 | 77 |
| 2015 | 47943 | 157 | 39 | 51 | 327 | 106 | 14613 | 71 | 8 | 8 | 486 | 55 |
| 2016 | 46109 | 116 | 12 | 13 | 252 | 28 | 12806 | 39 | 2 | 2 | 305 | 16 |
| 2017 | 23310 | 49 | 2 | 3 | 210 | 13 | 10891 | 15 | 2 | 2 | 138 | 18 |

* Rotavirus incidence rates are scaled as described in methods

Table 3: Incidence rate ratios (IRR) comparing rotavirus and diarrhoea incidence pre (Jan 2010-June 2014) and post vaccine (July 2014- June 2017) introduction in a vaccine impact study in Kenya 2010-2017*.

| | Post-vaccine period | IRR | Rotavirus | | All cause Diarrhoea | | |
|---------------|-------------------------|------|-----------|---------|---------------------|-----------|---------|
| | | | 95% CI | p-value | IRR | 95% CI | p-value |
| Kilifi | July 14- June 15 | 0.43 | 0.20-0.92 | 0.031 | 0.59 | 0.41-0.84 | 0.003 |
| | July 15- June16 | 0.20 | 0.07-0.54 | 0.002 | 0.52 | 0.45-0.60 | <0.001 |
| | July 16- June17 | 0.24 | 0.13-0.44 | <0.001 | 0.54 | 0.45-0.66 | <0.001 |
| Siaya | July 14- June 15 | 0.41 | 0.21-0.80 | 0.009 | 0.59 | 0.48-0.73 | <0.001 |
| | July 15- June16 | 0.18 | 0.08-0.39 | <0.001 | 0.40 | 0.28-0.57 | <0.001 |
| | July 16- June17 | 0.19 | 0.04-0.93 | 0.040 | 0.38 | 0.23-0.62 | <0.001 |

* See Methods for statistical details.

Figure 1

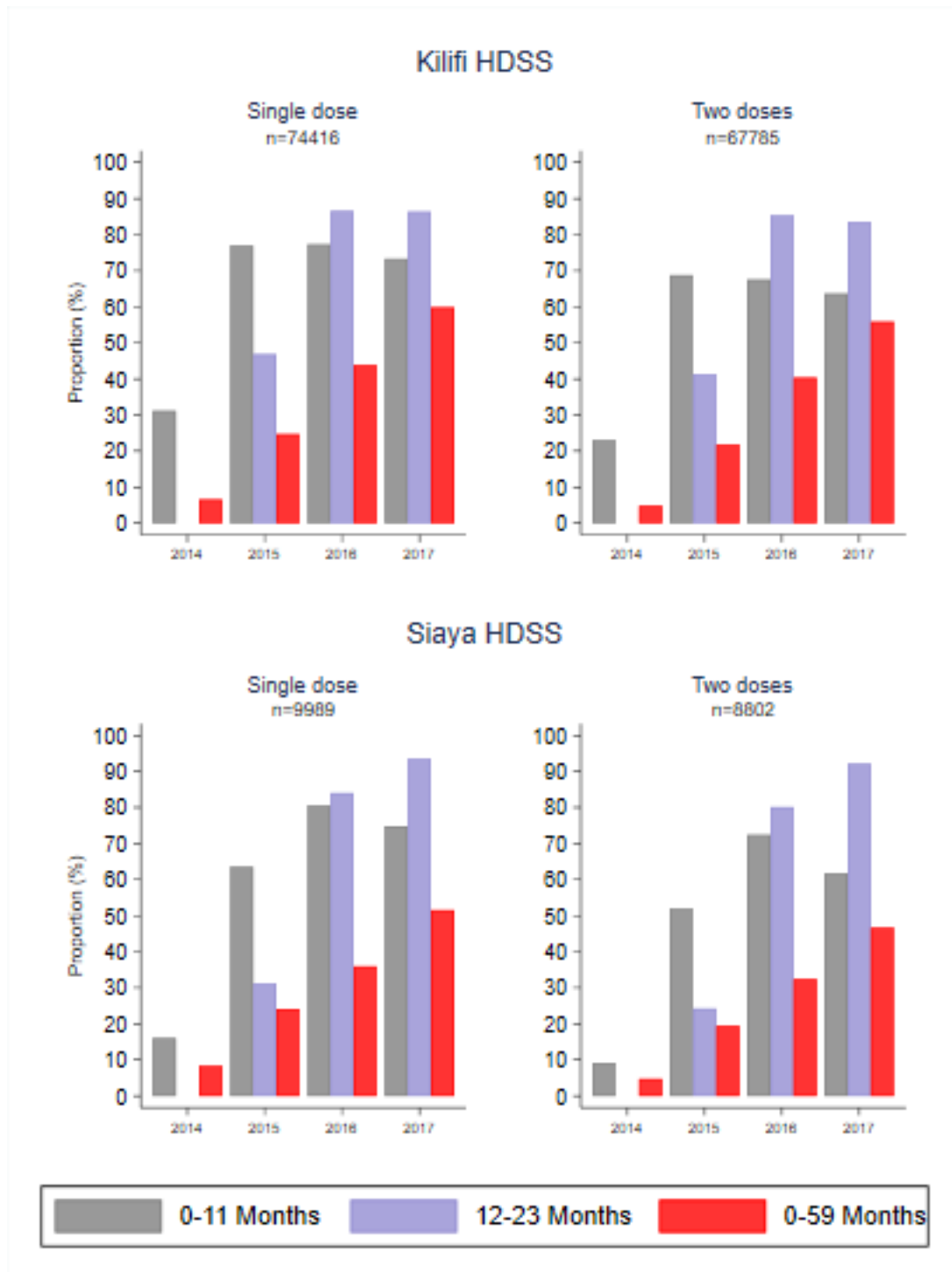


Figure 2

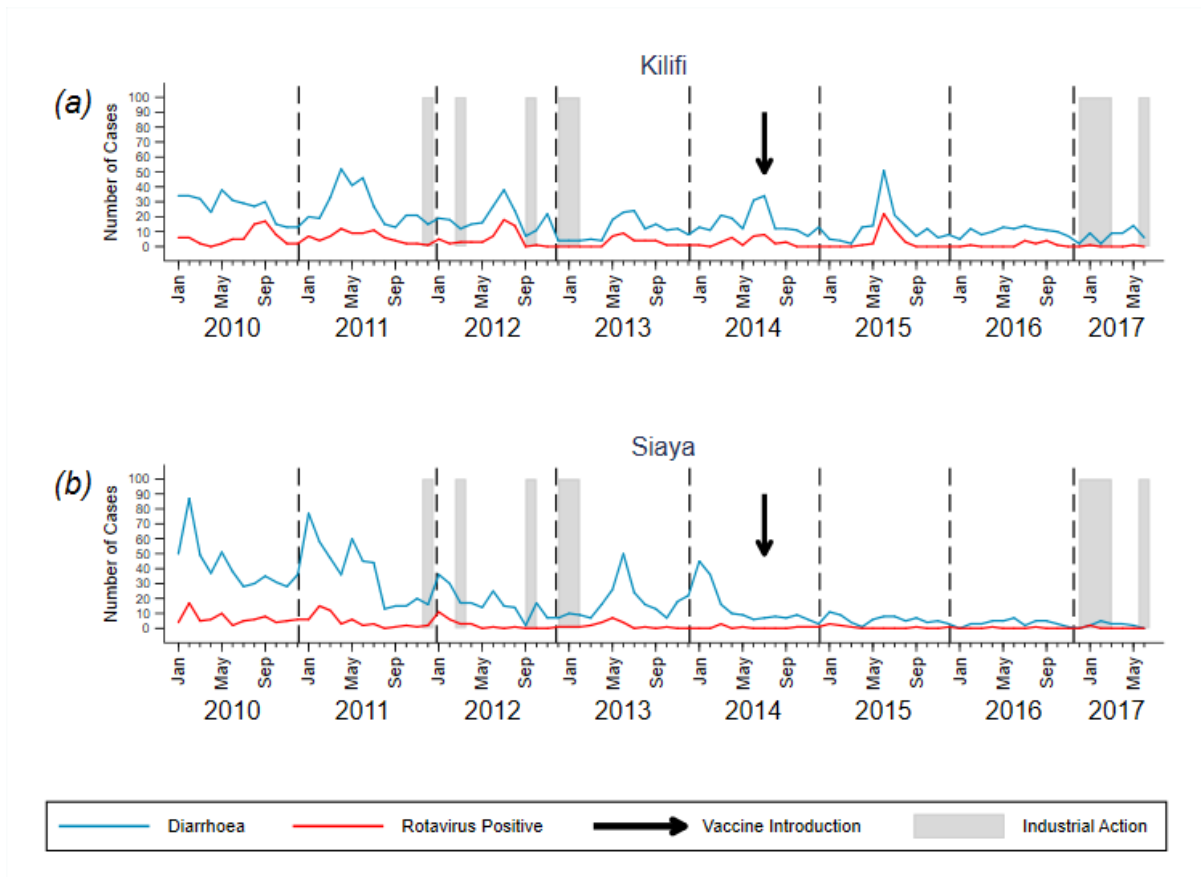


Figure 3

