Examining the impact of implementing routine rotavirus vaccination on the number of paediatric admissions due to diarrhoea and dehydration in Kenyan hospitals: A study using interrupted time series analysis.

Chelangat, Daisy; Malla, Lucas; Langat, Reuben C.; Akech, Samuel

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RESEARCH ARTICLE

REVISED Examining the impact of implementing routine rotavirus vaccination on the number of paediatric admissions due to diarrhoea and dehydration in Kenyan hospitals: A study using interrupted time series analysis.

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Previous title: The effect of introduction of routine immunization for rotavirus vaccine on paediatric admissions with diarrhoea and dehydration to Kenyan Hospitals: an interrupted time series study

Daisy Chelangat[1,2], Lucas Malla[3], Reuben C. Langat[2], Samuel Akech[1], Clinical Information Network Author Group

[1]Health Services Unit, KEMRI-Centre of Geographic Medicine Research-Coast/ KEMRI-Wellcome Trust Research Programe, Nairobi, Kenya
[2]Department of Mathematics and Computer Science, University of Kabianga, Kericho, Kenya
[3]Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, London, WC1E7HT, UK

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Abstract

Background

Dehydration secondary to diarrhoea is a major cause of hospitalization and mortality in children aged less than five years. Most diarrhoea cases in childhood are caused by rotavirus, and routine introduction of rotavirus vaccine is expected to reduce the incidence and severity of dehydration secondary to diarrhoea in vaccinated infants. Previously, studies have examined changes in admissions with stools positive for rotavirus but this study reports on all admissions with dehydration secondary to diarrhoea regardless of stool rotavirus results. We aimed to assess the changes in all-cause severe diarrhoea and dehydration (DAD) admissions following the vaccine's introduction.

Methods

We examined changes in admissions of all clinical cases of DAD before and after introduction of routine vaccination with rotavirus vaccine in

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1. **Mavuto Mukaka**, Mahidol University, Bangkok, Thailand
2. **Dan Hungerford**, University of Liverpool, Liverpool, UK
3. **Khitam Muhsen**, Tel Aviv University, Tel Aviv, Israel
4. **Tayebeh Latifi**, Emory University, Atlanta, USA

July 2014 in Kenya. We use data from 13 public hospitals currently involved in a clinical network, the Clinical Information Network (CIN). Routinely collected data for children aged 2-36 months were examined. We used a segmented mixed effects model to assess changes in the burden of diarrhoea and dehydration after introduction of rotavirus vaccine. For sensitivity analysis, we examined trends for non-febrile admissions (surgical or burns).

Results

There were 17,708 patients classified as having both diarrhoea and dehydration. Average monthly admissions due to DAD for each hospital before vaccine introduction (July 2014) was 35 (standard deviation: ±22) and 17 (standard deviation: ±12) after vaccine introduction. Segmented mixed effects regression model showed there was a 33% (95% CI, 30% to 38%) decrease in DAD admissions immediately after the vaccine was introduced to the Kenya immunization program in July 2014. There was no change in admissions due to non-febrile admissions pre-and post-vaccine introduction.

Conclusion

The rotavirus vaccine, after introduction into the Kenya routine immunization program resulted in reduction of all-cause admissions of diarrhoea and dehydration in children to public hospitals.

Keywords
Diarrhea, dehydration, time series, rotavirus, vaccine, clinical information network, multiple imputation.

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This article is included in the KEMRI | Wellcome Trust gateway.

5. **Flavia Kaduni Bawa**, University Ghana, Legon, Accra, Ghana

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Daisy Chelangat (daisichela@gmail.com)

Author roles: Chelangat D: Data Curation, Formal Analysis, Investigation, Methodology, Software, Visualization, Writing – Original Draft Preparation; **Malla L**: Conceptualization, Investigation, Methodology, Project Administration, Supervision, Validation, Writing – Review & Editing; **Langat RC**: Project Administration, Supervision, Validation, Writing – Review & Editing; **Akech S**: Conceptualization, Funding Acquisition, Methodology, Project Administration, Supervision, Validation, Writing – Review & Editing;

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REVISED **Amendments from Version 1**

The new version has generally been updated to make the manuscript more clear and address comments from reviewers. The manuscript title and abstract has been re-written to be more concise and clear.

The introduction section has been updated to capture more recent research and to provide a descriptive description of rotavirus vaccine coverage in Kenya. The methods section has also been updated to clearly describe the methodologies used in data collection as pointed out by reviewer.

Furthermore, additional sensitivity analysis was conducted to include a 2 months washout period when the vaccine was introduced and to include analysis for the different age groups in line with recommendations from reviewers. Additional visualizations of random effects were also added to show the change in all cause diarrhea and dehydration admissions across the different hospitals.

We've also uploaded 'Supplementary material 1: Missing data', and 'Supplementary material 2: Hierarchical negative binomial regression model' to a repository (see *Extended data*).

Any further responses from the reviewers can be found at the end of the article

Introduction

Diarrhoea, passage of three or more loose stools in one day, causes dehydration when fluid loss exceeds intake or replacement, and rotavirus is a predominant infectious cause of diarrhoea in early childhood (Kirk *et al.*, 2017). Globally, approximately 1.7 billion diarrhoea cases are reported every year amongst children aged less than five years (Heaton & Ciarlet, 2007). A survey in 2014 showed diarrhoea as the second leading cause of death in children aged less than five years in Kenya (Mulatya & Mutuku, 2020) and is also a major cause of illness and death in children in other sub-Saharan African countries. Vaccination is one of the measures recommended by WHO for reducing severe diarrhoea and diarrheal deaths (Kirk *et al.*, 2017). Most severe diarrhoea cases from rotavirus occur in children aged between two to 36 months (Fischer *et al.*, 2002) and studies indicate that after 36 months of age, most survivors obtain natural immunity from rotavirus infection even if they have not been vaccinated.

Rotavirus vaccine, administered orally to children at six and ten weeks, was introduced as part of the routine Kenya Expanded Immunization Program (EPI) in July 2014 (Wandera *et al.*, 2017). Studies investigating the impact of the routine introduction of rotavirus vaccine in Kenya have shown a reduction in rotavirus positive diarrhoea cases, but these studies have been based on surveillance of rotavirus in stools of children admitted to sentinel hospitals and therefore miss the critical secondary effects of rotavirus vaccine in all-cause diarrhoea admissions (Muendo *et al.*, 2018; Otieno *et al.*, 2020). In this study, we use routinely collected data to assess, using an interrupted time series design, the changes in all-cause severe diarrhoea admissions following the vaccine's introduction. The study population comprises children admitted with diarrhoea and dehydration to public hospitals.

Methods

Study area and setting

We use observational data collected from routine medical records from 13 public hospitals in Kenya participating in a Clinical Information Network (CIN). CIN is a collaboration to improve the collection and use of routine medical data to enhance the quality of care provided to admitted children through audit and feedback as previously described (Ayieko *et al.*, 2016; Gathara *et al.*, 2017; Irimu *et al.*, 2018a; Tuti *et al.*, 2016). The collaboration is between the KEMRI-Wellcome Trust Research Program (KWTRP), Kenya's Ministry of Health (MoH), the Kenya Pediatric Association, and participating county hospitals. Participation in the network by hospitals is voluntary but participating hospitals represent a wide geographical diversity of Kenya.

Data capture in CIN hospitals

Standardized paediatric admission record (PAR) forms are used to capture the patient's demographic and clinical details during admission, and discharge summary forms capture the patient's discharge details, including diagnosis, and whether they are discharged alive or dead. The medical forms are filed together with laboratory reports and other notes documented by the clinician and form part of patients' medical records. Participating hospitals have adopted these standardized forms as part of their routine medical records. Data is collected soon after the patient is discharged by abstracting data from the medical records into a dedicated database hosted in Research Electronic Data capture (REDCap), an open-source platform for capturing data (Harris *et al.*, 2009). Two categories of datasets are captured, minimum dataset and full dataset. Minimum datasets consist of information required for routine reporting to the ministry of health's health management information system (HMIS) and consists of the patient's demographic information, final diagnosis, and outcome (dead/alive). The full dataset consists of details on presenting history, admissions clinical assessment findings, admission treatments, details of investigations, and results of investigations. Minimum datasets are captured for children aged less than 30 days admitted to paediatric wards, surgical or burns admissions, and in randomized records in a few hospitals with high workload, and when the single data entry clerk is on leave for the high-volume hospitals (Irimu *et al.*, 2018b; Tuti *et al.*, 2016).

Participants

The study population comprises children between the age of two and 36 months admitted with diarrhoea and dehydration from September 2013 to November 2019.

Definitions of cases

Cases were identified as those with a discharge diagnosis of dehydration plus a history of diarrhoea or vomiting at admission (DAD-A) or presence of history of diarrhoea plus fulfilling criteria for signs of hypovolemic shock, severe dehydration or some dehydration (DAD-B). Severe dehydration is defined as presence of diarrhoea or vomiting with inability to drink or not alert plus either sunken eyes or return of skin pinch lasting

two seconds or longer. A child is termed to be in a hypovolemic shock if they have all the following signs-a weak pulse volume, not alert, have cold hands, capillary refill time longer than three seconds plus sunken eyes and slow return of skin when pinched in the presence of diarrhoea or vomiting. Lastly, some dehydration is defined as the ability to drink with two or more of sunken eyes, or skin pinch taking 1- 2 seconds in children with diarrhoea or vomiting (of Health, 2007).

Statistical data analysis

As a first step, only hospitals which had data consistently from 2013 were selected and admissions restricted to only those patients whose ages were between 2 and 36 months (Figure 1). We then selected those patients who either had a history of diarrhoea, vomiting, or a discharge diagnosis of diarrhoea or dehydration. Among the selected patients, there were those who were not indicated by the clinicians as having dehydration. We therefore used clinical signs recorded at admission to determine if children with history of diarrhoea met criteria for dehydration or shock as per the Kenya Basic Paediatric Protocols (MOH, Kenya, 2016). Signs used included pulse rate, capillary refill time, temperature gradient, sunken eyes, skin pinch, alertness, and ability to drink. We first assessed these signs for completeness in documentation as missingness is an inherent analytical challenge in routine datasets (Nicholls *et al.*, 2017) as shown in Table 1. Secondly, we conducted multilevel multiple imputation to account for clustering of data within the hospitals. We did fifteen imputations and ten iterations under Missing At Random (MAR) assumption (Schafer, 1999). Previous analysis of data from CIN hospitals have shown consistency with MAR assumption (Gachau *et al.*, 2019; Malla *et al.*, 2019). On each of the imputed datasets, we proceeded to (i) sum the number of patients with diarrhoea and dehydration per month, both as classified by the clinicians and identified by the algorithms, and (ii) fit segmented mixed effects model with autoregressive covariance structure and with the counts following negative binomial distribution. The segmented mixed effects model examined whether there were changes in DAD cases immediately (step change) and whether there were any significant month to month changes (slope change) after July 2014. There were widespread hospital worker's strikes between December 2016 to March 2017 and June 2017 to November 2017 and these strike periods were excluded in the analysis as there were very few to no admissions (Irimu *et al.*, 2018b). The modelling results across all the imputed datasets were pooled using Rubin rules (Little & Rubin, 2019).

Sensitivity analysis

In interrupted time series designs, it is critical to examine whether any changes observed would be attributable to the intervention under study and not any concurrent intervention(s) (López Bernal, 2018). We therefore examined changes in admission patterns of surgical/burn patients for comparison with DAD admission patterns. Surgical/burns admissions were selected from the same hospitals as that of DAD and were also aged between two to 36 months. We then fitted a segmented mixed effects regression model with the outcome also following a negative binomial distribution. Significant impact of rotavirus vaccine would be inferred in case of any differences in

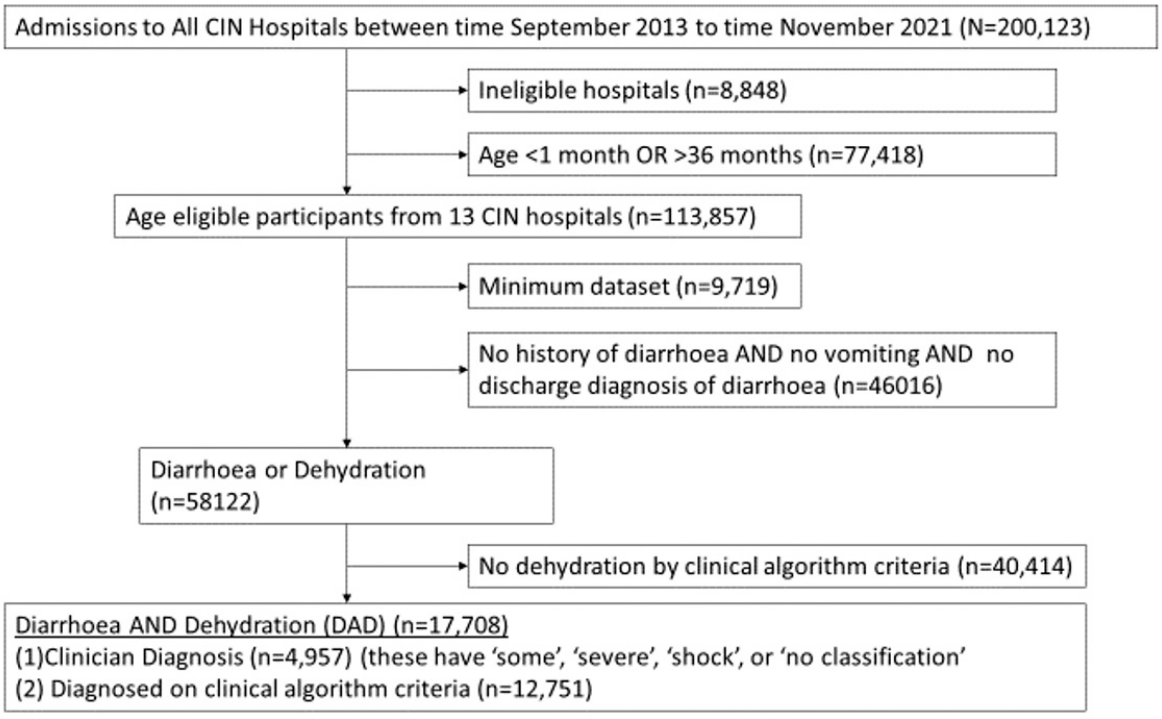

Figure 1. Patient inclusion criteria.

Table 1. Participant's summary statistics.

	Overall (n=17,708)	Before July 2014 n=3,429	After July 2014 n=14,297
Median Age in months, (IQR)	13.9 (8–18)	13.57 (8–18)	13.97 (8–19)
Gender			
Male, n (%)	55.6% (9746)	54.1% (1852)	54.8% (7835)
Female	44.4% (7962)	45.9% (1577)	45.2% (6462)
Monthly DAD admissions per hospital			
Mean (±SD)	19 (±15)	35 (±22)	17 (±12)
Median (IQR)	14 (9–23)	30 (17–45)	14 (9–21)
In-hospital deaths, n (%)	2.5% (4497)	1.7% (584)	2.7% (3,910)

step and slope changes in admission patterns between DAD and surgical/burn patients.

All the analyses were conducted using R version 4.0.0 (*R: A Language and Environment for Statistical Computing*, n.d.)

Ethics approval
Data used in this study is collected as part of routine medical records and individual patients' consent is not obtained. The Ministry of Health (Kenya) and participating hospitals have given permission for CIN collaboration, which involves sharing routine data with the research group. Clinical Information Network study has been approved by the Kenya Medical Research Institute (KEMRI) Scientific and Ethical Review Unit (SERU), which has approved use CIN data for observational research without individual consenting (SERU #2465 and #3459).

Results
Patient selection
A total 17,708 children admitted to the 13 hospitals between September 2013 to November 2019 met eligibility criteria for diarrhoea and dehydration (DAD) ad shown in Figure 1. Imputation was done in admissions who fulfilled had diarrhoea or dehydration as shown in Figure 1 before final selection of the 17,708 admissions with DAD. The proportion of missing data for various variables for the 58,122 admissions with diarrhoea or dehydration (see Figures) and proportion with various characteristics in the complete cases and imputed datasets are shown in Table 1. A comparison of the proportion with features of interest before and after multiple imputation showed no difference in the imputed dataset.

Participant's summary statistics
We present results for the 17,708 patients classified as having both diarrhoea and dehydration (DAD). Average monthly admissions due to DAD for each hospital before vaccine introduction (July 2014) was 35 (standard deviation: ±22) and 17 (standard deviation: ±12) after vaccine introduction as summarized in Table 2. Hospital admissions per month in different hospitals ranged from 6 to 100.

Changes in diarrhoea and dehydration after introduction of rotavirus vaccine
There was a 33.33% (95% Confidence Interval (CI): 15% to 45%) decrease (step change) in DAD admissions immediately after the vaccine was introduced to the Kenya Immunization Program in July 2014. The preceding 3.00% (95% CI: -3% to 9%) month to month change in slope in hospital admissions due to all-cause diarrhoea and dehydration was not statistically significant as presented in Table 3 and Figure 2.

Trends in surgical and burns admissions
We analysed 2,960 eligible admissions due to surgical or burns cases. The mean admissions of surgical or burns cases pre-intervention period was 41 patients (standard deviation ±12.72) and 36 patients (standard deviation ±8.16) post intervention. Our segmented negative binomial regression model showed no significant changes both in step and slope in hospitalization patterns due to burns (Table 4 and Figure 3) post July 2014 when the rotavirus vaccine was introduced. Change in month to month admissions (slope change) was -6% (95% CI: -38% to 2%) while step change was -25% (95% CI: -4% to 42%)

Discussion
This study reveals an overall reduction in hospital admissions due to all-cause diarrhoea and dehydration following the introduction of the rotavirus vaccine for children most at risk of rotavirus diarrhoea (2 to 36 months). Despite introduction of the vaccine in 2014, there remains significant admissions of cases of diarrhoea with stools positive for rotavirus in Kenya (Akech *et al.*, 2018; Muendo *et al.*, 2018; Nyaga *et al.*, 2018). Analyses specific to rotavirus positive cases from stool samples, seeking to evaluate vaccine performance, have shown reduction in hospitalization (Otieno *et al.*, 2020; Wandera *et al.*, 2017). Our study, which does not rely on rotavirus positive stool samples, further demonstrate benefit of introduction of rotavirus

Table 2. Interrupted time series analysis coefficients for diarrhea and dehydration admissions.

	Rate Ratios	95% confidence interval	P-value
Time	1.02	0.97 to 1.09	0.50
Step change	0.67	0.55 to 0.85	<0.01
Slope change	0.97	0.91 to 1.03	0.23

Note: Time - change in the slope of DAD admissions before July 2014; step change - change in admissions immediately after July 2014; slope change - change in the slope of admissions after July 2014.

Table 3. Interrupted Time Series regression coefficients showing change in admissions due to surgical or burns.

	Rate Ratios	95% confidence interval	p-values
Time	0.94	0.73 to 1.20	0.66
Step change	1.25	0.58 to 1.54	0.58
Slope change	1.06	0.98 to 1.38	0.65

Note: Time - change in the slope of burns admissions before July 2014; step change - change in admissions immediately after July 2014; slope change- change in the slope of admissions after July 2014.

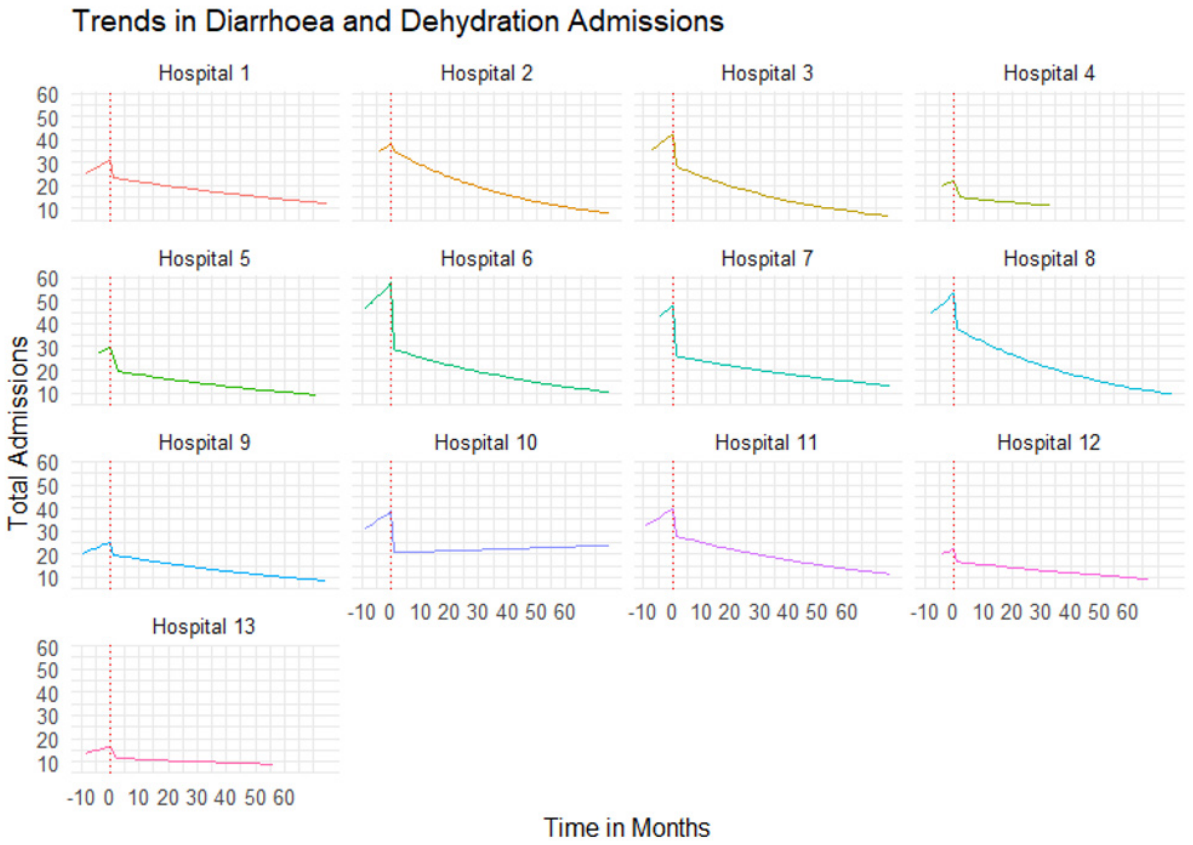

Figure 2. Trends in hospitalization due to diarrhea and dehydration. Note: Month Zero is when the vaccine was introduced into the national immunization program in Kenya.

Table 4. Change in admissions due to diarrhoea and dehydration following rota virus vaccine introduction for different age groups.

	2–11 months			12–23 months			24 – 36 months		
Predictors	***Rate Ratios***	***CI***	***p***	***Rate Ratios***	***CI***	***p***	***Rate Ratios***	***CI***	***p***
Time	1.01	0.97 – 1.05	0.65	1.00	0.97 – 1.04	0.89	1.03	0.98 – 1.08	0.29
Step change	0.76	0.60 – 0.96	**0.02**	0.95	0.77 – 1.17	0.62	0.94	0.72 – 1.23	0.65
Slope change	0.98	0.94 – 1.02	0.41	0.99	0.95 – 1.03	0.66	0.97	0.92 – 1.02	0.23

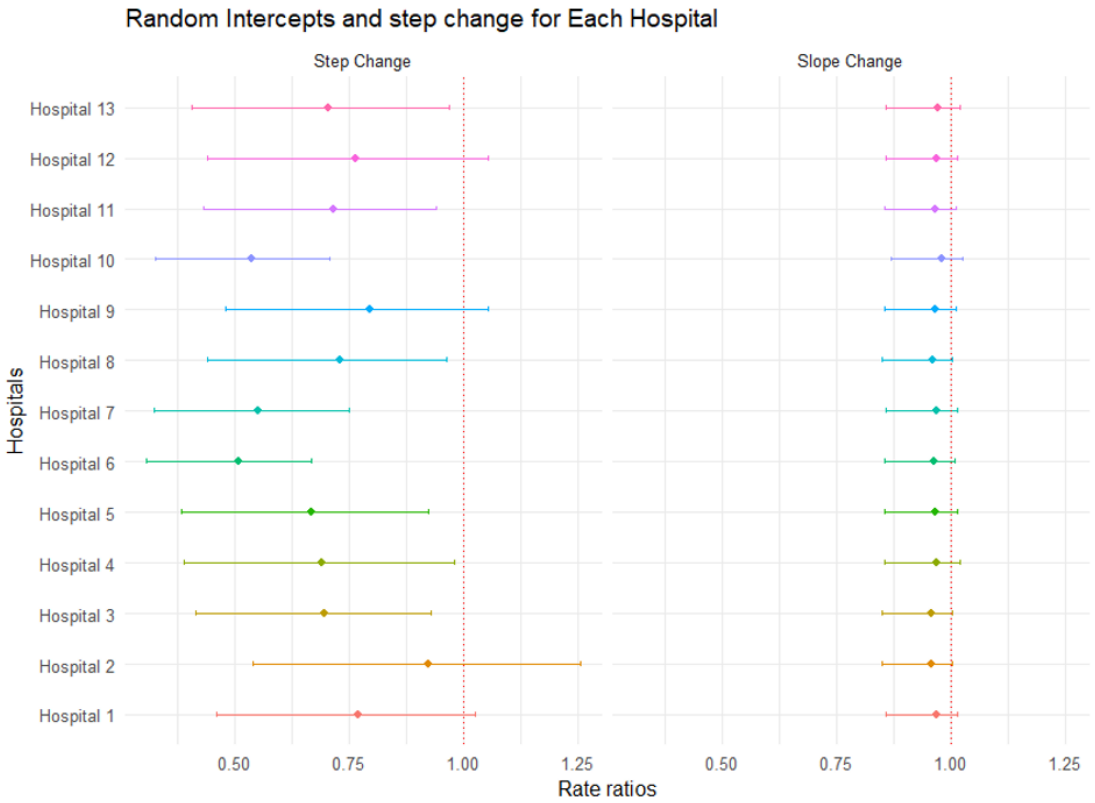

Figure 3. Random slope and step change for every hospital.

vaccine for reduction of cases of dehydration secondary to diarrhoea even in the absence of a stool test.

Pre-post analysis of the data showed a reduction in mean DAD hospitalization after the intervention. The fitted regression analysis model also showed an immediate reduction in all-cause DAD hospitalization following vaccination. This indicates an association between the change in children's volumes admitted to hospital due to all-cause DAD and the period of vaccine introduction. During the same study period, we observed no change in admissions with surgical/burns cases that were used as controls. This result is consistent to a study published in 2019 conducted in Kilifi county, Kenya (Otieno *et al.*, 2020). In the study, a surveillance was carried out for hospitalized children under the age of five and stools were tested for rotavirus. Data was collected from 2010 to 2017 which showed a significant effect of the vaccine in reducing rotavirus positive hospitalizations in the age group.

The results are also consistent with a recent study in Kenyan seeking to explore the prevalence of diarrhoea causing viruses in coastal Kenya before and after introduction of the rotavirus vaccine. Patients' stool samples were screened for different types of viruses and they showed that rotavirus prevalence had reduced post the intervention period (Wandera *et al.*, 2017). Our findings are in line with the results of a recent systematic review involving 34 sub-Saharan countries who had introduced the vaccine into their routine immunization

program where studies reporting rotavirus positive cases in children aged less than five years were included (Godfrey *et al.*, 2020). It was observed that there was a significant relationship with the reduction of rotavirus infection and use of the vaccine.

The main contribution of our study to the growing literature on the impact of rotavirus vaccine is that we use routine data collected from medical notes and demonstrate the impact of the vaccine in all-cause diarrhoea admissions. We show the value of routine hospital data to investigate impact of interventions, which could be valuable to supplement case control studies or surveys that often require significant resources to set up. Use of routinely collected data is cost effective, generalizable for severe cases with access to hospital care and they provide an attractive option for evaluation of effectiveness of interventions post implementation (Ayieko *et al.*, 2016; Irimu *et al.*, 2018a; Tuti *et al.*, 2016).

Our results are unlikely to be biased due to several reasons; we limited our analysis to children aged less than three years, the age most at risk of severe diarrhoea from rotavirus inflection. Diagnostics for multiple imputation showed that our imputation model yielded plausible values as shown in Table 1 where there is no difference in the proportion of observations with various characteristics post imputation.

This study assumes that patients use of the health facilities where not affected by other external factors in the two periods. However, significantly low admissions were recorded during the strike periods from December 2016 to March 2017 and July to November 2017. These periods were excluded from our study. We use data from 13 hospitals spread from across the country and admissions are unlikely to have been affected by localized factors such as establishment of major competing health facility. The pre-intervention period was eleven months which is shorter when compared to the 54 months post-intervention period. However, this is not a threat to validity of the analytic approach as many studies have shown that a minimum of ten datapoints was sufficient to detect change due to an intervention (López Bernal, 2018).

Conclusion

The rotavirus vaccine, after introduction into the Kenya routine immunization program, has resulted in reduced all-cause admissions of diarrhoea and dehydration in children aged less than 36 months to public hospitals in Kenya. The study demonstrates the value of routine hospital data for monitoring impact of interventions.

Data availability

Underlying data

Harvard Dataverse: CIN paediatric admissions, https://doi.org/10.7910/DVN/C0CDP9 (Chelangat *et al.*, 2021).

Data for this report are under the primary jurisdiction of the Ministry of Health in Kenya and are not openly available. The data used are available upon request by submitting a formal request through the KWTRP Data Governance Committee via email: dgc@kemri-wellcome.org. The details of the data access guidelines can be found on the KEMRI Wellcome Trust data repository (https://dataverse.harvard.edu/dataverse/kwtrp). Access can also be requested through Harvard Dataverse.

Extended data

B2SHARE: Supplementary material

10.23728/b2share.d3435ed0ce754f1ca4795a1458765c78 (Chelangat, 2025)

This project contains the following extended data:

- Supplementary material 1: Missing data
- Supplementary material 2: Hierarchical negative binomial regression model

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The Clinical Information Network (CIN) Author Group: Vihiga (Dr. Vitalis Juma, Samuel N'gar N'gar), Kakamega (Nick Aduro, Boniface Nyumbile, Roselyne Malangachi), Kisumu East County Hospital (Dr. Adem Achieng, Magdalene Kuria); Mbagathi County Hospital (Loice Mutai, Catherine Muendo, Christine Manyasi, and David Kimutai); Mama Lucy Kibaki County Hospital (Caren Emadau, Elizabeth Atieno Jowi, Cecilia Mutiso); Machakos County Hospital (Charles Nzioki and Supa Tunje); Nyeri County Hospital (Francis Kanyingi, Wagura Mwangi and Agnes Mithamo); Embu County Hospital (Sam Otido, Ann Kimunya and Esther Mukami Njiru); Kerugoya County Hospital (Dr. Mercy Kamau, Peninah Muthoni and Peris Njiiri); Kitale County Hospital (Rachel Inginia and Melab Musabi); Busia County Hospital (Emma Sarah Namulala, Barnabas Kigen, Yuvanne Maiyo); Kiambu County Hospital (Grace Akech and Lydia Thuranira). KEMRI-Wellcome Trust programme (Morris Ogero, Mercy Chepkirui, Cynthia Khazenzi, George Mbevi, Mike English, Grace Irimu, Ambrose Agweyu). Clinical Information Network team: David Githanga, Fred Were, Barnabas Kigen, Samuel NgarNgar, Nick Aduro, Rachel Inginia, Beatrice Mutai, Grace Ochieng, Lydia Thuranira, Francis Kanyingi, Margaret Kuria, Sam Otido, Kigondu Rutha, Peris Njiiri, Martin Chabi, Charles Nzioki, Joan Ondere, Caren Emadau, Cecelia Mutiso, Naomi Muinga, Michael Bitok, Timothy Tuti, Boniface Makone, Wycliffe Nyachiro, George Mbevi, Thomas Julius, Susan Gachau and Morris Ogero.

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Open Peer Review

Current Peer Review Status: ✔ ? ? ✘ ?

Version 2

Reviewer Report 07 February 2025

https://doi.org/10.21956/wellcomeopenres.25455.r117738

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Flavia Kaduni Bawa
Biochemistry, Cell and Molecular Biology, University Ghana, Legon, Accra, Ghana

Abstract: Can we say the immunisation program “contributed” to the reduction in admissions rather than “resulted in” since rotavirus is not the only cause of diarrhoea?

Methodology: It is unclear whether there was a mass vaccination of eligible children after the vaccine was introduced. At 9 months, most children would have taken most of their vaccinations requiring them to go to the vaccination centre less frequently. In this case, they would have missed the vaccination after completing their routine visits. Can you confirm whether these children were vaccinated in a mass vaccination? Otherwise, we cannot assume that children who came to the hospital after the vaccination program was rolled out were vaccinated. This could only be confirmed for those who turned 6 weeks after the vaccine introduction.

Does the strike period stated coincide with the peak seasons of rotavirus infections and could this have affected your results? This has been stated in the limitation but not compared to peak seasons

Results: If you have data for just one year before the vaccine was introduced, could you have analyzed for one year after the vaccine was introduced instead such that they would be comparable? Also, is it possible to show the monthly distribution of cases between pre and post-vaccination to compare peak seasons and changing trends?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases, febrile illness

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 30 January 2025

https://doi.org/10.21956/wellcomeopenres.25455.r117024

Mavuto Mukaka
Mahidol Oxford Research Unit, Mahidol University, Bangkok, Thailand

The authors have adequately addressed my comments. I have no further comments.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Statistics, epidemiology, malaria

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 20 January 2025

https://doi.org/10.21956/wellcomeopenres.25455.r117396

Tayebeh Latifi
Biochemistry, Emory University, Atlanta, Georgia, USA

While the rotavirus vaccine has reduced the number of rotavirus cases, it is important to recognize that rotavirus is not the only cause of diarrhea-associated deaths (DAD). Ignoring other potential agents introduces a bias in the study's conclusions.
As mentioned in the paper, many studies have already demonstrated a reduction in rotavirus cases and diarrhea following vaccine introduction. The authors need to clarify what is novel about their findings compared to existing literature.

Comments

Introduction

1. Mention the duration of the study (2013-2019).
2. Include the total number of patients (17,708) clearly.
3. In the background, correct the spelling of "diarrhea."

Methods

1. The paper states the study duration is 2014-2019, but this is not mentioned in the introduction. Ensure consistency.
2. Indicate how many of these cases received the rotavirus vaccine.

Results

1. Is there any significant difference between men and women before and after vaccination?
2. Specify what kind of rotavirus vaccine was used in those hospitals.
3. Figure 2: Note that the rotavirus vaccine and its type are not mentioned. Add more explanation to the figure legend.
4. What is the relevance of including surgical or burns cases? Why were these groups separated?

For table 4:

1. The legend does not explain the table very well. Add a more detailed presentation.
2. What is the logic behind making three different groups? What criteria were used?
3. Are the surgical and burns cases also from 2014-2019?

Additional Suggestions for Reliability: To enhance the reliability of the findings, compare the study's data with rotavirus-positive stool samples collected during the study period. This would strengthen the conclusions and provide additional context for the vaccine's impact.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Virology, Vaccine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Version 1

Reviewer Report 13 February 2023

https://doi.org/10.21956/wellcomeopenres.19260.r53843

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Khitam Muhsen
Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

The authors assessed the change in all-cause diarrhea and dehydration (DAD) hospital admissions after introducing universal rotavirus vaccination in Kenya (July 2014), using multicenter data of hospitalizations between September 2013 and November 2019.

The topic of this manuscript is of interest. Nonetheless, some concerns need to be addressed.

The authors used interrupted time-series analysis, but a limitation of this analysis is that there were very few data points before the introduction of rotavirus vaccination (September 2013 to July 2014).

It is important to describe the observed data (monthly or weekly number [and rates if possible] of DAD hospitalizations.

It is likely to take time to build up vaccinated birth cohorts in the community, accordingly is it possible to assume that there is a “transition period”, and not only “before and after periods”?

Can the authors provide information on rotavirus vaccination coverage in Kenya over time?

The changes in DAD before and after introducing universal rotavirus vaccination might vary with age groups since the vaccine is given to infants up to 32 weeks of age. Thus in the early period, the reduction might be of greater magnitude in infants than in toddlers. Therefore it is important to explore the change separately for different age groups (e.g. 0-11, 12-23, and 24-36 months).

Additional comments

Introduction – please provide up-to-date estimates (and references) of diarrheal disease burden.

Tables/ figures: there are typo errors. Legends should be added to explain the tables/abbreviations, and statistical analysis.

Table 2: instead of “mean monthly admissions per hospital” please present the median and interquartile range.

Table 3, under P value, instead of 0.00, please use <0.001.

In table 3 the authors presented odds ratios while in table 4 rate ratios. Please explain which models were used in each analysis.
Table 4: please correct “ration” to ratios

Figure 3: there is a discrepancy in the title: above the figure, it is written “trends in surgical or burns admissions”, while the title underneath the figure is” Figure 3. Trends in hospitalization due to diarrhoea and dehydration. Slope and level change in DAD hospitalizations over time”. Please check. In any case, this figure can be moved to supplementary material.

In figures 2 and 3, please explain what the y-axis stands for rate or absolute numbers, as well as what the different colors of the dots represent

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology of infectious diseases and vaccines, rotavirus vaccination impact

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 24 Sep 2024

Daisy Chelangat

Comment: The authors used interrupted time-series analysis, but a limitation of this analysis is that there were very few data points before the introduction of rotavirus vaccination (September 2013 to July 2014).

Response: We agree that the time we had a few timepoints before the introduction of the vaccine. However, from an analysis of literature it has been recommended for ITS studies to have at least eight time points pre-intervention(Ewusie et al., 2020). Our analysis had 10 timepoints which we believe provides a sufficient number.

Comment: It is important to describe the observed data (monthly or weekly number [and rates if possible] of DAD hospitalizations.
Response: We agree with this and a complete description of the CIN data including DAD data pre and post vaccine introduction have been added. “A total 200,123 paediatric patients were admited to CIN between September 2013 to November 2019 from 21

hospitals across Kenya. Admissions from eight out of twenty one hospitals were excluded from this study because they did not consistently have data from 2013 to 2019 (n = 8848). We further excluded 77,418 children who were not within our age range (1-36 months) in addition to 55735 who had only minimum data collected or no history of diahhrohea, no vomiting and no discharge diagnosis of diarrhoea (see Figure 1). A total of 58122 children were identified as having either dirrhoea or dehydration from which multiple imputation was applied to replace missing values. The proportion of missing data for various variables for the 58,122 admissions with diarrhea or dehydration and proportion with various characteristics in the complete cases and imputed datasets are shown in Table 1. A final sample of 17708 children met the eligibility criteria for diarrhea and dehydration (DAD). ….Average monthly admissions due to DAD for each hospital before vaccine introduction was 35 (standard deviation, SD: ±22) and 17 (SD: ±12) after vaccine introduction as summarized in Table 2. Hospital admissions per month in different hospitals ranged from 6 to 100."

Comment: It is likely to take time to build up vaccinated birth cohorts in the community, accordingly is it possible to assume that there is a "transition period", and not only "before and after periods"?
Response: We agree with this and an analysis including two months wash out period has now been added as part of the sensitivity analysis.

Comment: Can the authors provide information on rotavirus vaccination coverage in Kenya over time?
Response: an extensive description has now been added.

Comment: The changes in DAD before and after introducing universal rotavirus vaccination might vary with age groups since the vaccine is given to infants up to 32 weeks of age. Thus, in the early period, the reduction might be of greater magnitude in infants than in toddlers. Therefore, it is important to explore the change separately for different age groups (e.g. 0-11, 12-23, and 24-36 months).
Response: We agree with you on this and an analysis exploring change for each age group has now been added as a sensitivity analysis. Additional comments

Comment: Introduction – please provide up-to-date estimates (and references) of diarrheal disease burden.
Response: This has now been added

Comment: Tables/ figures: there are typo errors. Legends should be added to explain the tables/abbreviations, and statistical analysis.
Response: This has been corrected and explanatory notes added.

Comment: Table 2: instead of "mean monthly admissions per hospital" please present the median and interquartile range.
Response: Both mean and median monthly admissions including the interquartile range have now been added

Comment: Table 3, under P value, instead of 0.00, please use <0.001.

Response: This has been corrected

Comment: In table 3 the authors presented odds ratios while in table 4 rate ratios. Please explain which models were used in each analysis.
Table 4: please correct “ration” to ratios
Response: We regret this mix-up and has now been corrected to show rate ratios

Comment: Figure 3: there is a discrepancy in the title: above the figure, it is written “trends in surgical or burns admissions”, while the title underneath the figure is” Figure 3. Trends in hospitalization due to diarrhea and dehydration. Slope and level change in DAD hospitalizations over time”. Please check. In any case, this figure can be moved to supplementary material.
Response: We agree with you that there was a mix-up in naming and has been corrected.

Comment: In figures 2 and 3, please explain what the y-axis stands for rate or absolute numbers, as well as what the different colors of the dots represent
Response: We agree that this was not clear and has now been clarified

References Ewusie, J. E., Soobiah, C., Blondal, E., Beyene, J., Thabane, L., & Hamid, J. S. (2020). Methods, applications and challenges in the analysis of interrupted time series data: a scoping review. *Journal of Multidisciplinary Healthcare*, 411-423. Guillaume, D. A., Justus, O. O., & Ephantus, K. W. (2020). Factors influencing diarrheal prevalence among children under five years in Mathare Informal Settlement, Nairobi, Kenya. *Journal of public health in Africa, 11*(1).

Competing Interests: No competing interests were disclosed.

Reviewer Report 09 February 2023

https://doi.org/10.21956/wellcomeopenres.19260.r53844

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Dan Hungerford
Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool, UK

This study describes an ecological approach to assessing rotavirus vaccine impact on hospital admissions for diarrhoea with dehydration in Kenya across 13 hospitals. The analysis approach taken is an interrupted time-series analysis.

The study has major limitations.

There is less than one pre-vaccine season included in the time-series analysis (10 months). For a

time-series analysis to be robust for rotavirus there should be at least three seasons prior to vaccine introduction to allow for seasonal fluctuations.

In the limitations the authors state that there are 10 data points which they specify is sufficient. But these are contained within one / potentially two rotavirus seasons. Timing of data points is crucial e.g. 10 data points representing days may be suitable for one intervention (e.g. in an acute outbreak of something with a short incubation period) whereas 10 years may be needed for another. This is even more important for a non-specific endpoint like DAD, where other pathogens may account for high numbers in the year preceding vaccine, were there any outbreaks of other enteric pathogens in 2013/14?

Therefore, the authors should try and provide evidence from other studies in Kenya that yearly DAD admissions were at a consistent level prior to rotavirus vaccine introduction and that there were no enteric pathogen outbreaks or high seasons in the year prior to vaccine introduction.

Another way to improve confidence in the findings would be to conduct an analysis of children 0-1 years of age as rotavirus vaccine impact would be expected to be greatest in this age group (see citation).

Please could the authors also justify why an offset/denominator was not used in the model - using either total monthly admissions or catchment population size for the age group.

There is no detail provide on population level vaccine uptake. This needs to be included in either the introduction as statements or ideally if data are available provided in the methods and results. If available there should also be regionally coverage figures provided as the study includes data from 13 hospitals.

Other comments
Abstract - Please add the study time period. Otherwise the abstract appears to be hiding the fact that there is limited pre-vaccine data.

Introduction
The reference for global diarrhoea cases is very old, either put in context that this is prior to rotavirus vaccine licensure or add a more recent estimate.

Please also add detail that children experience many infections (symptomatic and asymptomatic) after first severe infection and immunity has variable waning by setting.

Add some detail and references on the VE / impact of vaccination on rotavirus AGE in Kenya.

Please also add a sentence or two on impact from other relevant countries - this provides useful context for the reader.
Need to add context that the majority of severe infections will occur in children <2 years.

Please add detail on which rotavirus vaccine is used in Kenya.

Methods
Please detail what coefficients / epi measures were generated from the models and how 95% CIs

were generated.

Results
Table 3 presents odds ratios and table 4 rate rations? please clarify and as stated above specify transformation of coefficients in the methods.

References

1. Bergman H, Henschke N, Hungerford D, Pitan F, et al.: Vaccines for preventing rotavirus diarrhoea: vaccines in use.*Cochrane Database Syst Rev*. 2021; **11** (11): CD008521 PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: I report grants on the topic of rotavirus vaccines from GlaxoSmithKline Biologicals, Sanofi Pasteur and Merck and Co (Kenilworth, NJ, USA) after the closure of Sanofi Pasteur-MSD in December 2016.

Reviewer Expertise: Infectious disease epidemiology - focusing on GI. Specifically real world vaccine evaluations of rotavirus vaccines.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 17 January 2022

https://doi.org/10.21956/wellcomeopenres.19260.r47771

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Mavuto Mukaka
Mahidol Oxford Research Unit, Mahidol University, Bangkok, Thailand

The effect of introduction of routine immunization for rotavirus vaccine on paediatric admissions with diarrhoea and dehydration to Kenyan Hospitals: an interrupted time series study.

The authors tackle an important area. However, there are a number of issues that must be addressed to improve the quality of this manuscript.

Major:

- In the abstract, the authors state that they used a segmented mixed effects model, but the statistical model used is not mentioned. They should state the statistical model.

- The authors state that they conducted multilevel multiple imputation to account for clustering of data within the hospitals. I thought the primary aim of multiple imputation is to address the missing data issue and not for accounting for clustering. Unfortunately, the authors do not state this primary aim of multiple imputation. It seems like there is a mix up of things. In that case which data was missing and was multiply imputed?

- For accounting for clustering, multilevel (hierarchical) models are relevant and authors need to state the type of statistical hierarchical model that was used and state the different levels of clustering.

- From the write-up, it is very difficult to capture the nature of the outcome. Table 3 provide odds ratios but logistic regression has never been mentioned anywhere in the text. Similarly, Table 4 provide rate ratios, are these incident rate ratios? Can the authors indicate in the table the model that was used to obtain these ratios? Was the outcome binary or count data?

- There is a mixed up between results and discussion. For example, in the results section about Changes in diarrhoea and dehydration after the introduction of rotavirus vaccine, the authors present the results in terms of percentage and 95% confidence intervals for the percentage change. However, the table being referred to presents odds ratios and 95% confidence intervals for the odds ratios. The authors should present the results as presented in the tables and they can make these other types of interpretations in the discussions. Presenting like this can easily confuse the readers when they crosscheck against the tables.

- Table 3, Level change is 1.25, 95% CI as 0.58 to 1.04. Why is the estimate 1.25 higher than the upper limit of the 95% CI i.e. 1.04?

- Figure 3 is a spaghetti plot of individual trajectiles, can the authors include the line that describes the overall trend i.e. the mean over time.

- Sensitivity analyses are described in the abstract and in the methods section but they seem not to be presented in the results section and discussed in the discussion section. The authors should present and discuss these.

- Authors should consider a brief section describing Missing at Random, Missing Not at Random and Missing completely at random definitions to help justify why Missing at Random was considered as a reasonable assumption.

Minor:

- Figure 1 says between “2013 and 2011”. It does not make sense to me. Please correct this. I do not see where 2011 is coming from.

- In table 4, the authors write “rate rations” instead of “rate ratios”.

- Table 2 misses some key variables including gender.

- P-values of 0 and 0.0 in the table are not meaningful. These p-values are conventionally presented as <0.001 etc. because the p-value cannot be exactly 0. It is also better to be consistent in the number of decimal places.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Statistics, epidemiology, malaria

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 24 Sep 2024

Daisy Chelangat

The Effect of Introduction of Routine Immunization for Rotavirus Vaccine on Paediatric Admissions with Diarrhoea and Dehydration to Kenyan Hospitals: An Interrupted Time Series Study

Reviewer comments Major:

Comment: In the abstract, the authors state that they used a segmented mixed effects model, but the statistical model used is not mentioned. They should state the statistical model. **Response:** We have added the model that was used in the analysis "To assess the impact of the rotavirus vaccine on DAD admissions, we applied a segmented mixed-effects negative binomial regression model". Page 2

Comment: The authors state that they conducted multilevel multiple imputation to account for clustering of data within the hospitals. I thought the primary aim of multiple imputation is to address the missing data issue and not for accounting for clustering. Unfortunately, the authors do not state this primary aim of multiple imputation. It seems like there is a mix up of things. In that case which data was missing and was multiply imputed?
Response: We agree with the reviewer that the aim of multiple imputation was not clear. We have clarified this and also given the justification for multilevel multiple imputation. "We then performed multilevel multiple imputation to impute missing data, accounting for potential clustering of missingness within the hospitals". Page 6

Comment: For accounting for clustering, multilevel (hierarchical) models are relevant, and authors need to state the type of statistical hierarchical model that was used and state the different levels of clustering.
Response: This has been corrected in the manuscript "fitting a segmented mixed-effects negative binomial regression model with an autoregressive covariance structure and a log link function to examine step and slope changes in DAD admission counts". Page 6

Comment: From the write-up, it is very difficult to capture the nature of the outcome. Table 3 provide odds ratios but logistic regression has never been mentioned anywhere in the text. Similarly, Table 4 provide rate ratios, are these incident rate ratios? Can the authors indicate in the table the model that was used to obtain these ratios? Was the outcome binary or count data?
Response: The outcome variable has now been clarified "In this study, we use routinely collected data and an interrupted time series design to assess changes in all-cause severe diarrhoea admissions following the introduction of the vaccine,". Page 3. It has been clarified in the tables that we are presenting results from an "Interrupted time series analysis coefficients for diarrhea and dehydration admissions" (Table 2). For the odds ratios, a negative binomial mixed effect regression model with a log odds link function gives odds ratio estimates for coefficients.

Comment: There is a mixed up between results and discussion. For example, in the results section about Changes in diarrhoea and dehydration after the introduction of rotavirus vaccine, the authors present the results in terms of percentage and 95% confidence intervals for the percentage change. However, the table being referred to presents odds

ratios and 95% confidence intervals for the odds ratios. The authors should present the results as presented in the tables and they can make these other types of interpretations in the discussions. Presenting like this can easily confuse the readers when they crosscheck against the tables. **Response:** We agree that there is a mix up and the discussion section has been re-written for clarity. Page 12

Comment: Table 3, Level change is 1.25, 95% CI as 0.58 to 1.04. Why is the estimate 1.25 higher than the upper limit of the 95% CI i.e. 1.04?
Response: This was a typing error from the previous section and has now been corrected and is in Table 3; Level change is 1.25 and the 95% CI is 0.58 to 1.54

Comment: Figure 3 is a spaghetti plot of individual trajectiles, can the authors include the line that describes the overall trend i.e. the mean over time.
Response: A graph that now describes overall trend along side the individual trajectories has now been added in the same panel (Figure2 and 3).

Comment: Sensitivity analyses are described in the abstract and in the methods section but they seem not to be presented in the results section and discussed in the discussion section. The authors should present and discuss these.
Response: In the results and discussion sections, the sensitivity analysis is presented but not clearly. An extensive description of a couple of sensitivity analyses is now presented.

Comment: Authors should consider a brief section describing Missing at Random, Missing Not at Random and Missing completely at random definitions to help justify why Missing at Random was considered as a reasonable assumption.
Response: A section describing different mechanisms of missing data has now been added as a supplementary material

Minor:
Comment: Figure 1 says between “2013 and 2011”. It does not make sense to me. Please correct this. I do not see where 2011 is coming from.
Response: this was a typing error and has been corrected in Figure 1 which now reads: “September 2013 to November 2021”

Comment: In table 4, the authors write “rate rations” instead of “rate ratios”.
Response: This was a typing error and it now reads: “rate ratios”. Table 2

Comment: Table 2 misses some key variables including gender.
Response: Variable gender has now been added and is now presented in Table 1

Comment: P-values of 0 and 0.0 in the table are not meaningful. These p-values are conventionally presented as <0.001 etc. because the p-value cannot be exactly 0. It is also better to be consistent in the number of decimal places.
Response: This is now corrected, and p values now reads “<0.01”. The number of decimal places is now also consistent across the manuscript.

Competing Interests: No competing interests were disclosed.