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# The Impact of Rotavirus Vaccine Introduction: An Exploratory Analysis of Case Statistics in Kenya, Zimbabwe and Senegal

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Master of Public Health

Global Epidemiology

_____

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By

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B.A., Wake Forest University, 2015

Thesis Committee Chair: Dr. Benjamin Lopman, MSc, PhD

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# Abstract

The Impact of Rotavirus Vaccine Introduction: An Exploratory Analysis of Case Statistics in Kenya, Zimbabwe and Senegal

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Ty R. Kraniak

Among diarrheal diseases, rotavirus exhibits a large burden of disease despite the usage and endorsement of safe and effective vaccines. The impact of rotavirus vaccine introduction and usage has been documented by various sources. This paper seeks to demonstrate the various effects of rotavirus vaccine introduction in Kenya, Zimbabwe, and Senegal by examining reported case statistics prior to vaccine introduction, during the year of vaccine introduction, and in the year following vaccine introduction. Vaccine effects such as protection for unvaccinated individuals in populations that have introduced rotavirus vaccine are demonstrated by a 59% case reduction (compared to pre-introduction averages) among unvaccinated 0-1 month olds in the three aforementioned countries combined. Additionally, a simple linear regression model found that on average case ages increased by 12.6 and 12.9 weeks in Kenya and Zimbabwe (respectively) when comparing ages of cases in the three years prior to vaccine introduction to case ages in the year following vaccine introduction. However, in Senegal, cases became 8.1 weeks younger on average in the year following vaccine introduction. These results are largely consistent with previous studies, and despite their limitations, can assist in immunization planning activities.

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# Table of Contents

# Introduction

## Rotavirus Epidemiology

Childhood deaths due to diarrheal illnesses remain a concern in many countries' quest for improving health and inducing economic development. Among diarrheal diseases, complications stemming from rotavirus represent a substantial share of deaths. 2016 estimates attribute over 125,000 annual deaths to rotavirus with the majority of deaths occurring in sub-Saharan Africa. In 2016 alone, rotavirus caused more than 258 million diarrheal events worldwide among children less than five years (with an incidence of .42 cases per child year). This substantial burden occurs even though rotavirus vaccines saved over 28,000 lives of under five year old children in 2016 (1). Apart from safe and effective rotavirus vaccines endorsed by the World Health Organization, improving water and sanitation, zinc supplementation, oral rehydration salt usage, and improving case management are recommended to reduce rotavirus cases (2). To prevent disease, rotavirus vaccine is administered orally as RotaTeq (given as 3 doses at 2, 4, and 6 months) or Rotarix (given as 2 doses at 2 and 4 months) and has been recommended as the most effective prevention technique against the disease (3). Although rotavirus cases have decreased in recent years partly due to vaccine introduction, the global burden of disease is still influential.

Rotavirus demonstrates various patterns in its global epidemiologic burden. Rotavirus displays seasonal discrepancies in temperate climates (such as Europe and North America), while sustained transmission often occurs throughout the entire year in

more tropical countries (4). In addition, case age distribution shows typically earlier primary cases in low income countries (80% occur among children under 1 year of age) in comparison with high income countries (65% occur among children under 1 year of age) (5). Furthermore, approximately 90% of all deaths associated with rotavirus occur in Asian and African nations, pointing toward geographic disparities in rotavirus mortality (6).

## Vaccine Effects

Rotavirus vaccines confer both direct and indirect effects. Direct effects of a vaccine lower the illness susceptibility of those who receive the vaccination (7). Mameli et al's systematic review found that the effectiveness of rotavirus vaccine changes with location, generally showing lower effectiveness in low income countries. Reasons for the differing direct effect estimates include: presence of maternal antibodies, co-infection, malnutrition, and simultaneous dosage given with the oral polio vaccine. Additionally, the review also concluded that vaccine effectiveness declined during the second year of life, especially in locations with high mortality (8).

Rotavirus vaccines may also provide indirect effects. Indirect effects are defined as the protection of unvaccinated individuals in a population (which is known as herd protection). When a vaccine is introduced into a population, the number of infectious individuals will decrease as a result of the direct effects of vaccination, which will also decrease the force of infection. Therefore, the indirect benefit is derived through the decreased probability of an un-vaccinated individual coming into contact with a contagious individual, as vaccination decreases the infected number in a population (9).

As direct effects vary upon location with rotavirus, indirect effects also depend largely on location as they involve dynamic parameters. These parameters include: the transmission patterns of the pathogen, immunity parameters derived from vaccination, mixing patterns in the community, and the vaccination distribution and patterns, among other factors (10). Therefore, as these parameters change depending on location, the risks of infection as well as the indirect effects also change with geography. With rotavirus' force of infection higher in low income settings, we can expect the indirect effects to be lower in these settings as well.

The indirect effects of rotavirus vaccine have been quantified through a number of studies. As detailed in a systematic review, indirect vaccine effectiveness was quantified to be 52% in high income countries and 25% in low and middle income countries (11). Estimates from the United States also provide important information concerning indirect effects. It was estimated that 15% of the total hospitalizations and 20% of the medical costs averted by vaccination were among those unvaccinated in an older age group, as a result of indirect effects (12). A study in Ontario also demonstrates evidence supporting indirect vaccine effects, where the model suggests that elderly unvaccinated individuals receive protection against attending hospitals for acute gastroenteritis by those vaccinated (RR=.80) (13). Finally, modeling predictions suggest that following the first year of vaccine introduction, rotavirus incidence would decrease by double the amount that was predicted by direct effects alone (assuming a 90% vaccination coverage rate) (14).

To complement the direct and indirect effects previously mentioned, total and overall vaccine effects also represent important concepts in vaccine epidemiology.

Overall vaccine effects are the difference in outcome of an average individual in a population receiving an intervention in comparison with an individual in a population not receiving an intervention (15). When studied, these concepts help re-inforce the benefits of various vaccines.

## Age Shifts

Following rotavirus vaccine introduction, age shifts of cases have been observed in various settings. With rotavirus, age shifts occur partly due to a sometimes lower indirect vaccine effectiveness among older children and also the lack of a catchup campaign to vaccinate older children who were ineligible to receive routine immunization (16). Additionally, a lower force of infection is connected with age shifts of cases (17). The age-related epidemiological shift may have negative effects for diseases such as hepatitis A, rubella, and varicella where the disease is known to worsen with older cases or with diseases that have multiple serotypes (18). However, older cases are often less severe with rotavirus, where risk was found to decrease with age after controlling for antibody levels (19). A study in Rwanda found that in the four years following rotavirus vaccine introduction, there were significant age shifts in hospitalizations of diarrhea cases to older age groups. In 2011, 56% of rotavirus hospitalizations were among children under 1 year old, while that proportion decreased to 41% in 2015 (20). As these age shifts may undermine benefits made by a vaccination program, epidemiological transitions should be noted and monitored for improved disease control and prevention.

This paper seeks to examine the various effects of vaccine introduction as well as the changes in age distributions of cases in three African countries (Kenya, Senegal, and Zimbabwe) following rotavirus vaccine introduction in 2014. Specifically, we examine the reduction in cases among both vaccinated and unvaccinated individuals in the aforementioned countries by comparing case statistics before, during, and after vaccine introduction. Additionally, we consider the age shifts of rotavirus cases through a comparison of pre-vaccine introduction case statistics and post-vaccine introduction case statistics.

# Methods

## Data Source

To address our research aims, data were analyzed from previously compiled rotavirus case statistics from 2011-2015. Rotavirus cases and their respective age in weeks, location (according to country), and year of occurrence were compiled by Hasso-Agopsowicz et al. from a number of academic (through conducting a PRISMA systematic review), governmental, as well as WHO surveillance sources to provide reported rotavirus cases (21). WHO GRSN database was utilized as a primary surveillance network for compiling cases, and it includes statistics regarding hospital admissions in over 60 countries of children under 5 years of age (21, 22). This surveillance network was launched in 2008 in connection with the Global Rotavirus Laboratory Network, where specimens are lab tested after sentinel hospital sites identify individuals whom meet a standardized case definition for rotavirus (23). More detailed

instructions regarding dataset compilation are provided by Hasso-Agopsowicz et al. in the respective citation (21).

From this original dataset, rotavirus case statistics were limited to those occurring in Kenya, Senegal, and Zimbabwe from 2011-2015 for this analysis. These countries were selected based on their year of vaccine introduction, which occurred in 2014 for all three nations (24). All case statistics are personally de-identified, and thus the researchers of this paper received an exempt status from Emory University's IRB team, who made the determination for this analysis as non-human subject research.

## Vaccine Effects

To calculate overall vaccine effects, cases were summed across country, year, and age (where age brackets were determined based on vaccination schedules and also burden of disease) utilizing Microsoft Excel 2016 and SAS Statistical Software 9.4. Additionally, aggregate rotavirus cases across Kenya, Senegal, and Zimbabwe were summed across national vaccination status (identified as pre-introduction of vaccine, year of vaccine introduction, and year of post-vaccine introduction) to calculate cases relative to the population vaccination status. Within each age bracket, averages of cases per month were calculated to standardize the quantification of case counts. Additionally, case percent reductions were calculated by dividing the decrease of average monthly cases from before vaccine introduction by the average monthly pre-vaccination case count within the respective age bracket.

## Age Shifts

*Descriptive Analysis*

In addition to quantifying the overall vaccine effects, descriptive statistical analysis was performed to demonstrate the age shifts in rotavirus cases occurring after vaccine introduction. The number of cases per country and according to national vaccination status were aggregated and summed. The mean and standard deviation were then calculated according to country and national vaccination status. Additionally, cases from the three countries were plotted graphically by dividing the number of cases per age in weeks by the total number of cases in each national vaccination status grouping.

*Simple Linear Regression*

In addition to the descriptive analysis, simple linear regression was undertaken to quantify age shifts. Separate models were considered for each individual country as differing countries represent different characteristics and a possible source of confounding. The models represent how much, on average, a national vaccine introduction status shifts the average age of rotavirus cases in each country. In other words, the model can be written as: average age of rotavirus cases in weeks = $\alpha + \beta$ (country level vaccination status). Additionally, no additional confounding variables were considered or assessed, and therefore, no correlation analyses occurred.

*Outcome Variable*

The age of rotavirus cases (both countries combined as well as country specific) was used as a primary outcome variable for the regression analysis. This was measured by the age in weeks of the child when he/she was diagnosed with rotavirus, and this

metric was provided for each case by the original data source referenced above. The regression coefficient thus represents the average change in age (measured in weeks) of cases compared to pre-vaccine introduction, and the 95% confidence intervals were calculated for each parameter.

*Explanatory Variable*

The primary explanatory variable of interest for regression analysis was the year in which each rotavirus case occurred, which signifies the national status of vaccine introduction. The national status was classified as either pre-vaccine introduction, year of vaccine introduction, or the year following vaccine introduction based on the year when the respective case occurred. All three nations introduced their rotavirus vaccines in 2014, and therefore, all case data in 2014 was classified as the year of vaccine introduction. Therefore, all cases occurring from 2011 to 2013 were in pre-vaccination populations, where no children were vaccinated (discounting migration). All cases occurring in 2015 were in post-introduction of vaccine populations, such that the majority of one annual birth cohort was vaccinated.

# Results

## Vaccine Effects

Overall, 2,702 rotavirus cases were included in our analysis from Senegal, Kenya, and Zimbabwe spanning from 2011 to 2015 (Table 1). Among our prescribed age brackets, infants among 6-11 months experienced the largest case count with a total of

1,150 cases across all three countries combined, of which 193 cases occurred after vaccine introduction. Additionally, there was a reduction from 39.3 cases per month in the unvaccinated 6-11 month age group prior to vaccine introduction to 32.2 cases per month in the 6-11 month vaccinated age group in the year after vaccine introduction, representing an 18% reduction in cases. The reductions in case counts among age groups expected to receive vaccination help support rotavirus vaccine's success in reducing disease.

We also observed a reduction from 8.5 average cases per month among unvaccinated 0-1 month olds prior to vaccine introduction to 3.5 cases per month among unvaccinated 0-1 month olds in a population that introduced rotavirus vaccine the year before, signaling a 59% reduction (Table 1). This demonstrates protective effects for unvaccinated newborns. However, among children who were too old to be vaccinated against rotavirus in 2014 or 2015 (24-59 months), there was an increase from 1.1 cases/month before vaccination introduction to 1.5 cases/month in the year following vaccine introduction, representing a 36% increase in cases.

Finally, when comparing total cases across years, there was a slight reduction in overall cases from 566 average cases per year before vaccine introduction to 536 cases in the year after following vaccine introduction, which resulted in a 5% case reduction across all children under 5 years. Additionally, there was a 17% case reduction when comparing the number of cases during the year of vaccine introduction to the average cases per year before the three countries introduced rotavirus vaccine in 2014.

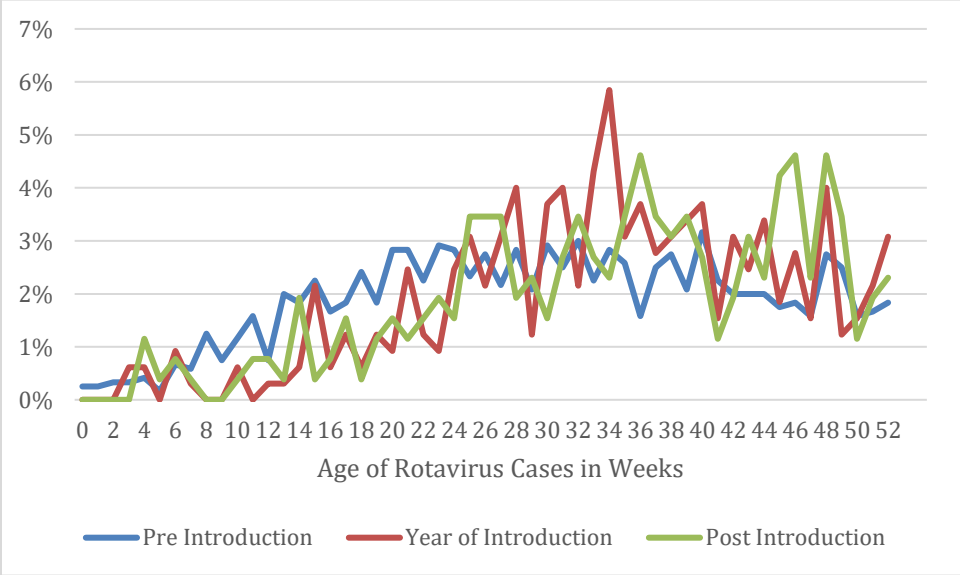
Table 1: Rotavirus cases under 5 years old by national vaccine introduction status and age: Kenya, Senegal, and Zimbabwe combined

| | 0-1 Months | 2-5 Months (During Scheduled Vaccination) | 6-11 Months | 12-17 Months | 18-23 Months | 24-59 Months | Totals |
|---|---|---|---|---|---|---|---|
| 2011 | 28 (14) | 140 (35) | 224 (37.3) | 82 (13.7) | 33 (5.5) | 40 (1.5) | 547 |
| 2012 | 19 (9.5) | 188 (47) | 260 (43.3) | 116 (19.3) | 46 (7.7) | 32 (1.2) | 661 |
| 2013 | 4 (2) | 114 (28.5) | 224 (37.3) | 105 (17.5) | 32 (5.3) | 12 (.5) | 491 |
| Total Pre-vaccination | 51(8.5) | 442 (36.8) | 708 (39.3) | 303 (16.8) | 111 (6.2) | 84 (1.1) | 1,699 (566) |
| 2014 (Year of Vaccine Introduction) | 8 (4) | 68* (17) | 249* (41.5) | 99 (16.5) | 25 (4.2) | 18 (.7) | 467 |
| % Reduction from Cases in Pre-Vaccine | 53% | 53% | -5% | 2% | 32% | 36% | 17% |
| 2015 | 7 (3.5) | 60* (15) | 193* (32.2) | 170* (28.3) | 66* (11) | 40 (1.5) | 536 |
| % Reduction from Cases in Pre-Vaccine | 59% | 57% | 18% | -68% | -77% | -36% | 5% |
| Totals | 66 | 570 | 1150 | 572 | 202 | 142 | 2,702 |

Age Distribution

Figure 1 shows the proportion of rotavirus cases by age (measured in weeks) according to the national vaccination status. This aggregate graph demonstrates the proportion of cases within each national vaccination status group according to their age. The graph shows a higher proportion of older cases after rotavirus was introduced, which exemplifies a shift in cases to older populations.

Figure 1: Proportion of rotavirus cases by vaccine introduction status according to age




*Descriptive Analysis*

The average case age was 45.6 weeks (SD 32.3) for the three countries combined during the three years before vaccine introduction (Table 2). Senegal experienced the oldest average cases with an average of 47.1 weeks before vaccine introduction. During the year of vaccine introduction, the average age across the three countries increased to 47.0 (SD 27.3) weeks on average. Following the year of vaccine introduction, the average age of cases increased to 58.0 (SD 31.6) weeks when combining statistics from Kenya, Senegal, and Zimbabwe.

*Simple Linear Regression Results*

Despite the overall increase in mean case age following rotavirus vaccine introduction, variation was observed among the individual countries. In Zimbabwe, we observed a statistically significant increase of 12.9 (95% CI: 9.6, 16.1) weeks in the

average age of rotavirus cases when comparing the post-vaccine introduction year statistics to pre-vaccine introduction periods. Similarly, Kenya observed an increase of 12.6 (95% CI: 4.7, 21.5) weeks in the average age of rotavirus cases when comparing pre-vaccine introduction years to case statistics observed in the year following rotavirus vaccine introduction. However, contrary to the other countries, we observed a decrease in Senegal of 8.1 (95% CI: -33.2, 17.0) weeks in the average rotavirus case age when comparing pre-vaccine introduction statistics to cases in the year following vaccine introduction. This result was not significant at $p < .05$ level.

Table 2: Age of cases in weeks according to vaccine introduction status and country

| Pre-Vaccine Introduction (2011-2013) | N (Cases) | Mean | SD | Change in Age (Weeks) of Cases from Pre-Vaccine Introduction (Regression Coefficient) | 95% C.I. |
|---|---|---|---|---|---|
| Senegal | 87 | 47.1 | 39.3 | - | - |
| Kenya | 306 | 47.9 | 36.6 | - | - |
| Zimbabwe | 1306 | 45.0 | 30.7 | - | - |
| Total | 1,699 | 45.6 | 32.3 | - | - |
| Year of Vaccine Introduction (2014) | | | | | |
| Senegal | 20 | 35.3 | 23.1 | -11.9 | -29.6, 5.9 |
| Kenya | 69 | 55.8 | 40.7 | 8.0 | -1.5, 17.4 |
| Zimbabwe | 378 | 46.0 | 23.9 | 1.1 | -2.3, 4.5 |
| Total | 467 | 47.0 | 27.3 | 1.4 | -1.8, 4.6 |
| Post Vaccine Introduction (2015) | | | | | |
| Senegal | 9 | 39.0 | 23.3 | -8.1 | -33.2, 17.0 |
| Kenya | 108 | 60.5 | 30.6 | 12.6 | 4.7, 21.5 |
| Zimbabwe | 419 | 57.8 | 32.0 | 12.9 | 9.6, 16.1 |
| Total | 536 | 58.0 | 31.6 | 12.4 | 9.4, 15.5 |

# Discussion

As result of the descriptive analysis as well as simple linear regression, we conclude three main findings. First, there was protection for children aged 6-11 months when comparing pre-vaccine introduction statistics with the year following vaccine introduction, signifying protection for age groups receiving vaccination. Additionally, we observed protection for unvaccinated 0-1 month olds during the year following vaccine introduction, suggesting indirect effects for young unvaccinated infants. Finally, there were overall significant age increases when comparing the year following vaccine introduction to the pre-vaccine introduction years in all three countries combined.

## Vaccine Effects

Various effects of introducing rotavirus vaccine were observed in Senegal, Zimbabwe and Kenya in our analysis. Reductions in cases among vaccinated age groups were observed when compared to similar aged populations prior to vaccine introduction. For example, an 18% case reduction was found when comparing likely vaccinated 6-11 month olds with non-vaccinated 6-11 month olds in populations yet to introduce the vaccine. However, cases in 2015 (when compared to pre-vaccine introduction averages) increased among children 12-17 and 18-23 months in age (who may have been vaccinated in 2014) by 68% and 77%, respectively. As rotavirus vaccine was introduced at varying points during 2014, many of these individuals may or may not have been vaccinated. These estimates compare with a case reduction of 43% when examining rotavirus case counts three years post vaccine introduction in Malawi (when comparing

cases in the same three months of the year to adjust for the seasonality of disease). However, there was no reduction in cases during the first year after vaccine introduction in Malawi (25).

Additionally, we observed a 59% case reduction among unvaccinated 0-1 month olds during the year after vaccine introduction compared to the same age group before vaccine introduction. This signifies indirect effects for the unvaccinated children in partially vaccinated populations. However, among children between 24-59 months (who were too old to be vaccinated in 2014 or 2015), there was a 36% increase in cases, which helped shift the average age of cases to older populations. Reductions of rotavirus cases among unvaccinated individuals in vaccinated populations have been observed in other settings as well. In Malawi, Bennet et al. found that among unvaccinated children with gastroenteritis (truncated at 24 months), rotavirus prevalence decreased from 53% in the 10 months before rotavirus vaccine introduction to 35% in the 14 months following vaccine introduction, which shows significant protection for unvaccinated children. Similar to our analysis, Bennet et al. did not find protection for unvaccinated children of older age groups (12-59 months) in the 36 months after vaccine introduction (26). This analysis thus helps demonstrate amplified effects of vaccination programs beyond the reported coverage, although such effects were relatively minor in scope.

Age Shifts

Our analysis also showed a statistically significant increase in the average age of rotavirus cases in the year following vaccine introduction in Zimbabwe and Kenya. This is consistent with findings in Malawi that documented an increase of roughly a month

and a half in the median age of rotavirus cases following vaccine introduction (26). The protection of vaccinated individuals would thus increase the average age of cases by providing protection among those vaccinated, which would usually occur between 2-5 months. Additionally, our analysis demonstrated that older children are not experiencing as much protection when compared to younger children, which would shift the average case age to older children.

Even though we observed significant increases in the mean age of rotavirus cases in the year following vaccine introduction in Kenya and Zimbabwe, Senegal experienced a decrease in its average age of rotavirus cases. Even though Senegal has a comparable average age of rotavirus infection prior to vaccine introduction when compared to Kenya and Zimbabwe, Senegal's cases unexpectedly became younger after vaccine introduction. However, this decrease in average age is accompanied by a large standard error of 12.65, is not statistically significant, and is driven by a very low case count of 9 cases in the year following vaccine introduction. With such a large standard error and a small case count, caution is warranted when interpreting Senegal's results.

Limitations:

There were various limitations to the data as well as analysis performed in this analysis. Primarily, the underreporting of cases were a primary limitation as only the most severe cases were likely reported in the hospital surveillance indicators (and therefore included in the dataset used for this analysis). Additionally, the dataset only included cases from a few sentinel sites in each country. Despite the underreporting, the distributions of cases according to age and national vaccine introduction status should be

relatively representative of national statistics. As this was a time series analysis, unaccounted biases that change over time may have influenced the results of this study. Additional external factors that affect case counts according to age could be a caretaker's willingness to bring younger infants more frequently to the hospital, resulting in a reported case. Finally, only one year of post vaccine introduction data was included in this analysis due to the availability of data. This sometimes resulted in few cases observed, such as Senegal's statistics where 9 cases were observed in the year following vaccine introduction (which results in low statistical power). Furthermore, the lack of case data following vaccine introduction limited this analysis from understanding how vaccine effects change over multiple post vaccine introduction years. For example, in Tanzania, diarrheal hospitalizations were 26% in two years post vaccine introduction and 58% lower in three years following vaccine introduction at the Dodoma Regional Referral Hospital (27). Based on trends observed in other countries, it is likely that the protective vaccine effects would increase as more birth cohorts are vaccinated and high coverage is achieved in Kenya, Zimbabwe, and Senegal.

Public Health Impact/Future Directions

Despite the limited analysis to Kenya, Senegal, and Zimbabwe, there may be additional value of this study. The knowledge of the existence of overall vaccine effects allows countries to more appropriately plan and execute effective vaccination programs. Additionally, the knowledge of protection among unvaccinated individuals allows countries to more accurately evaluate the cost effectiveness of rotavirus vaccines (26). Finally, the shifting age patterns of rotavirus cases following vaccine introduction can

better inform rotavirus prevention programs to reach more appropriate populations. Ultimately, additional research in differing countries (with more years of data following vaccine introduction) should be conducted to confirm these findings with greater statistical power in order to improve the generalizability of this study and incorporate new findings.

## Conclusion

Through analyzing the data of rotavirus cases in Kenya, Zimbabwe, and Senegal, we were able to demonstrate evidence of various forms of vaccine effects by examining reductions of rotavirus cases in various populations. This supports other existing evidence concerning the benefits of vaccination in reducing case counts. Additionally, statistically significant increases in the average age of rotavirus cases following vaccine introduction were found in Kenya and Zimbabwe, while Senegal observed a non-significant decrease in the average age of rotavirus cases following vaccine introduction. These findings largely support previous evidence in other locations, and they can inform more targeted rotavirus prevention strategies.

Conflicts of Interest: None

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