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Assessment of Rotavirus Vaccine Type and Number of Doses on Severity of Disease

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ABSTRACT

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Assessment of Rotavirus Vaccine Type and Number of Doses on Severity of Disease
(Under the direction of Dr. Lisa Casanova, Faculty Member)

Background: Rotavirus disease is the leading global cause of severe diarrhea in children under 5 years. We examined the association between different rotavirus vaccines doses and severity of diarrhea.

Methods: A secondary analysis of surveillance of children with acute gastroenteritis (AGE) symptoms during two seasons (January-June) in 2010 and 2011 from three pediatric hospitals in Atlanta, Georgia was conducted. Enrolled children were tested for rotavirus, using EIA (Rotaclone) and vaccination records were collected from the state immunization registry and healthcare providers. Cases were defined as any enrolled child who tested positive for rotavirus. Each enrolled child was assigned a Vesikari score to assess AGE severity.

Results: 63.9% of participants had severe AGE. Cases were more likely to have severe AGE than controls (OR 3.8, 95% CI: 2.2-6.5). Receiving a mixed vaccine regimen had similar protection against severe disease to receiving only RotaTeq® or Rotarix® (Mixed: OR 0.1, 95% CI: 0.02-0.5; RotaTeq®: OR 0.1, 95% CI: 0.02-0.5; Rotarix®: OR 0.1; 95% CI 0.01-0.3). When controlling for vaccine type and demographic covariates, three doses of vaccine offered significant protection against severe disease (OR 0.3, 95% CI: 0.2-0.6).

Conclusions: Receiving a mixed regimen of rotavirus vaccine is effective in preventing severe AGE. Mixed rotavirus vaccine regimens were equally efficacious to receiving a single type of vaccine in preventing severe disease. Three doses of vaccine, regardless of type, were effective in preventing severe disease but one or two doses were not.

ASSESSMENT OF ROTAVIRUS VACCINE TYPE AND NUMBER OF DOSES ON SEVERITY OF DISEASE

By

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"...And my success is not but through Allah. Upon Him I have relied, and to Him I return." -The Holy Quran (11:88)

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1. "Rotavirus Vaccination Disparities Seen Among Infants with Acute Gastroenteritis (AGE)." Trisha B Chan, Nana Wilson, Khushdeep Malhotra, Saadia Khizer, **Anaam Mohammed**, Shabnam Jain, Philip Spandorfer, and Lilly C Immergluck. Pediatric American Societies Annual Meeting. Washington, DC. May 4, 2013.
2. "Virulence Factors Associated with MRSA USA300 Carriage In Children with Skin and Soft Tissue Infections (SSTIs)." Lilly Immergluck, Shabnam Jain, **Anaam Mohammed**, Kevin Thornton, Mark Brice, Trisha Chan, and Sara Satola. Pediatric American Societies Annual Meeting. Washington, DC. May 4, 2013.
3. "COMPARE: Choosing Opiod Management for Pain and Analyzing ACS Rates Equally." ID Buchanan, T Chan**, A Mohammed**, S Khizer. Atlanta, GA. January 21, 2012.

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CHAPTER I:

INTRODUCTION

1.1 Background

Rotavirus remains the leading cause of severe diarrhea in children under the age of five worldwide. In 2008, rotavirus was responsible for 453,000 deaths among children younger than five.[20] Rotavirus is the most common organism which causes gastroenteritis in children. Deaths due to rotavirus overwhelmingly occur in developing countries, with approximately 85% of all rotavirus deaths occur in Africa and Asia. The World Health Organization estimates that rotavirus diarrhea results in approximately half a million deaths and approximately 2.4 million hospitalizations in developing countries each year.[2]

There are currently two widely used rotavirus vaccines: Rotarix® (GlaxoSmithKline Biologicals), a human, live attenuated 2-dose vaccine and RotaTeq® (Merck), a live, oral pentavalent 3-dosevaccine.[2] Rotavirus vaccines have been included in the regular immunization schedule for children in the US since 2006. Efficacy of RotaTeq® and Rotarix® ranges from 39% to 77% in developing countries, such as those in Africa and Asia.[3] Several studies conducted in the United States have reported considerable reduction in illness caused by rotavirus after the introduction of rotavirus vaccines. Similarly, a greater number of rotavirus vaccine doses have been associated with reduction in disease complications.[8] In developed countries, rotavirus vaccines have demonstrated high efficacy against severe rotavirus disease (pooled efficacy =85%).[9] A recent study of the effectiveness of both rotavirus vaccines in Spain revealed no significant differences between RotaTeq® and Rotarix®.[10] The efficacy of mixed doses has not been previously assessed.

1.2 Purpose of Study

To determine the effect of receiving Rotarix®, RotaTeq®, or a mixed dose of the vaccines on the severity of rotavirus disease, this secondary analysis of a case-control study of participants from Children's Healthcare of Atlanta hospitals was undertaken. The purpose of this study was to examine the association between the type and number of doses of rotavirus vaccine and the severity of disease in children under three.

1.3 Research Questions

1. Does the type of rotavirus vaccine children receive (RotaTeq® vs. Rotarix® vs. mixed) affect the severity of their disease as measured by the Vesikari scale?
2. Does the number of doses of rotavirus vaccine children receive affect the severity of their disease as measured by the Vesikari scale?

CHAPTER II:

LITERATURE REVIEW

2.1 Burden of Rotavirus Disease

Rotavirus is the leading cause of severe diarrhea in children under the age of five worldwide. By the age of five, nearly every child in the world has been infected with rotavirus at least once.[1] Deaths due to rotavirus occur disproportionately in developing countries, with approximately 85% of all rotavirus deaths occurring in Africa and Asia.[2] Prior to the introduction of the rotavirus vaccines, over 40% of pediatric hospital admissions for diarrhea worldwide were caused by rotavirus infections.[10]

Similarly, United States hospital discharge database, the Healthcare Cost and Utilization Project (HCUP) data was used to extrapolate that rotavirus was the cause of ~60,000 hospitalizations and 37 deaths in the US annually.[16] Before the introduction of rotavirus vaccines in the US, 410,000 doctor's visits, 70,000 hospitalizations, and 272,000 Emergency Department (ED) visits were attributed to rotavirus annually. This burden represented a societal cost of close to $1 billion.[23]

In 2007, rotavirus diarrhea was associated with an estimated annual healthcare cost of $319 million and a total annual cost to society of $893 million.[17] The rotavirus gastroenteritis-associated hospitalization burden is substantial, both in terms of the number of hospital visits and the cost.[18]

2.2 Disparities in Rotavirus Disease in the United States

Although national introduction of both RotaTeq® and Rotarix® has caused an overall decline in rotavirus gastroenteritis hospitalizations in children of all races, the same disparities in

rotavirus disease observed in pre-vaccine years persist in the US. Particularly, race and insurance status account for some of the disparities.[16-18] For example, the Medicaid population had a disproportionate number of hospitalizations from rotavirus gastroenteritis than non-Medicaid populations.[18]

Adjusting for age, Black children were found to have a lower visit rate for diarrhea associated illness than White children in outpatient setting but a higher visit rate for diarrhea-associated illness in the ED setting. Conversely, Whites had a significantly greater (40%) rate of healthcare utilization for diarrhea-associated illness outpatient clinics than Blacks, but Blacks utilized the ED for diarrhea-associated illness at nearly double the rate of Whites. These data suggest that race may influence site of care for diarrhea-associated illness in children.[17] Similarly, data from HCUP found that Black infants had a significantly higher risk of being hospitalized and dying from rotavirus early in life, when compared to Whites.[16]

2.3 History of Rotavirus Vaccines

The first rotavirus vaccine was introduced in 1998. RotaShield® (Wyeth) was a tetravalent vaccine that contained the G1-G4 rotavirus strains. After clinical trials that proved it to be 80-100% effective in preventing severe diarrhea, RotaShield® was licensed for use in the US. However, it was later discovered to have possibly contributed to an increased risk for intussusception in one in every 12,000 vaccinated infants, and was therefore, removed from the market in 1999.[20]

In 2006, two new rotavirus vaccines were introduced: RotaTeq® and Rotarix®.[2,10] In the US, the rotavirus vaccines were first recommended for all children in February 2006. Three years later, the World Health Organization Strategic Advisory Group of Experts recommended the rotavirus vaccine for all children. As of 2011, Rotarix® had been introduced into 27 national

vaccine programs, and RotaTeq® had been introduced into 7national vaccine programs. Some countries, such as the US and Australia offer both vaccines, whereas others have switched from RotaTeq® to Rotarix® or vice versa or have still not introduced the vaccines.[7,10] It is estimated that introduction of rotavirus vaccines in low-income countries would prevent 45% of deaths and approximately 58% of associated medical visits and costs due to rotavirus.[24]

Tracking intussusception rates before (2000-2005) and after (2007-2009) the introduction of RotaTeq® and Rotarix®, Yen and colleagues found a small increase in intussusception rates have been seen among infants aged 8-11 weeks with the first dose of the current rotavirus vaccines. Despite this, no population level changes in rates of intussusception hospitalizations have been noted.[15]

In March 2010, porcine circovirus-1 (PCV-1) was identified in the Rotarix® vaccine. PCV-1 infects pigs but is not known to cause infections in humans. Still, the US Food and Drug Administration suspended use of Rotarix®. Further testing of both rotavirus vaccines revealed that RotaTeq® contained small amounts of PCV-1 and PCV-2, another porcine circovirus strain. The Rotarix® ban was removed by the FDA later in 2010 because the PCV strains pose only a theoretical risk to humans, as there has been no documented human infection by PCV strains.[25]

2.4 Differences between Rotarix® and RotaTeq®

	RotaTeq ® (RV1)	**Rotarix ® (RV5)**
Manufacturer	Merck	GlaxoSmith Kline Biologicals
Conception	Live, oral pentavalent	Human, live attenuated
Antigenic Composition	G1, G2, G3, G4, P1A ressortant strains from bovine strain WC3 (type G6P7[5])	G1P1A[8] from the human strain 89-12
Number of Doses	3	2
Schedule	2, 4, and 6 months (first dose should be given within	2 and 4 months (first dose should be given within

	6-15 weeks of age and the last dose by 8 months of age, with at least 4 weeks in between doses)	6-15 weeks of age and the last dose by 8 months of age, with at least 4 weeks in between doses)

Adapted from Lopman, et al., 2012.

2.5 Rotavirus Vaccine Efficacy

Introduction of the rotavirus vaccines has been associated with reductions in gastroenteritis mortality.[7] Substantial reductions in rotavirus hospitalizations in middle and high-income countries have been observed as well. In high-income countries, including the US, Australia, Austria, Spain, and Israel, vaccine effectiveness was >85%, similar to that of clinical trials.[10, 26-29] In upper middle-income Latin American countries, such as Mexico and Brazil, vaccine effectiveness varied from 79 to 94%.[30-32] Effectiveness in El Salvador, a low middle-income country, was 76%, not much different than the effectiveness in higher middle-income countries.[33]

In developing countries in Africa and Asia, the efficacy of RotaTeq® and Rotarix® ranges from 39-77%. Though the efficacy of rotavirus vaccines is lower in developing countries than developed ones, the indirect vaccine benefits, such as herd immunity, are especially important in developing countries. These indirect benefits help to reduce transmission of rotavirus within the community. After the introduction of the rotavirus vaccines in low-middle and middle income Latin American countries, deaths and hospitalizations due to rotavirus decreased.[3] Specifically, clinical trials in the high-mortality, low–income countries of South Africa and Malawi found a significant decrease in severe diarrheal episodes due to rotavirus after the introduction of the vaccine. [2] This suggests that similar reductions will take place in other high-mortality, low-income countries.

Wang and colleagues assessed the effectiveness of RotaTeq® following partial completion of the 3-dose regimen. One dose of RotaTeq® was associated with being 88%

effective against preventing rotavirus gastroenteritis hospitalizations and ED visits and 44% effective against preventing all gastroenteritis hospitalizations and ED visits. Two doses of the vaccine were associated with 94% effectiveness in preventing rotavirus gastroenteritis hospitalizations and ED visits and 40% in preventing all gastroenteritis hospitalizations and ED visits. This illustrates that RotaTeq ® is effective against rotavirus even before a full vaccine regimen in complete.[4] Likewise, another study found that RotaTeq® begins to protect children against hospitalizations and ED visits for rotavirus gastroenteritis as early as 14 days after the first dose and between doses as well.[5]

Few rotavirus vaccine efficacy studies have addressed both RotaTeq® and Rotarix® or a mixed vaccine regimen.

2.6 Vesikari Scale

The Vesikari scale was developed in 1990 to assess diarrheal disease severity. It measures the duration of diarrhea, the maximum number of stools in a 24 hour period, the duration of vomiting, the maximum number of vomiting episodes in a day, temperature, dehydration, and treatment. The Vesikari scale is a widely accepted 20-point scale, in which a score of 1-10 indicates non-severe disease, and a score of 11 or above indicates severe disease.[12] It has been used to assess disease severity in vaccine efficacy studies of both RotaTeq® and Rotarix® in the US, Latin American, African, Middle Eastern, Asian, and European countries.[13,21-22]

CHAPTER III:

METHODOLOGY

3.1 Study Design

The methodology of this case-control study has been described elsewhere.[11] Briefly, active acute gastroenteritis (AGE) surveillance was conducted from January through June of 2010 and for the same period during 2011 in the Emergency Departments (ED) and inpatient floors at the three Children's Healthcare of Atlanta (CHOA) hospitals. Parents of children who presented with a complaint of diarrhea were approached for enrollment. Patients were eligible for enrollment if they were: (1) diagnosed with acute gastroenteritis (AGE) defined as ≥ 3 looser than normal stools within a 24-hour period and diarrhea < 10 days at time of enrollment; (2) managed as an ED patient, short-stay patient, or inpatient; (3) had no immunocompromising condition (e.g. malignancy, HIV infection); (4) had a stool sample collected from the patient within 14 days of presentation of illness with results available from a rotavirus antigen immunoassay; (5) eligible to have received at least 1 RV dose ≥14 days before presentation according to birth date (6) born on or after March 1, 2009 and age at evaluation ≥56days; and (7) lived in the usual catchment area of the hospital.

Rotavirus testing on stool specimens was conducted at the Centers for Disease Control and Prevention (CDC) using commercial enzyme immunoassay (EIA) kit (Rotaclone) to determine whether patients were rotavirus positive (cases) or rotavirus negative (controls).

This study was approved by institutional review boards of Morehouse School of Medicine, CDC and CHOA.

3.2 Study Measures

Severity of disease was determined using the Vesikari scale. The Vesikari scale measures duration of diarrhea, maximum number of diarrheal episodes in a 24 hour period, duration of vomiting, maximum number of vomiting episodes in a 24 hour period, temperature, dehydration, and treatment. The Vesikari scale is a 20-point scale in which a score of $\geq$11 is considered severe. A score of 1-10 on the Vesikari scale is considered not severe. Patients were, therefore, classified as having severe or non-severe disease.[12-14] Severe and non-severe patients were further categorized based on whether they received Rotarix®, RotaTeq®, or a mixed vaccine regimen and how many doses of rotavirus vaccine they received. Vaccine information was obtained from the state immunization registry and provider records.

3.3 Study Definitions

Vaccine Type

Participants were grouped into vaccine type cohorts based on their vaccine history at the time of illness, which was obtained from provider records and the state immunization registry. Participants categorized as RotaTeq® or Rotarix® only received that respective vaccine, regardless of the number of doses received. Receiving a mixed vaccine dose was defined as receiving at least one dose of RotaTeq® and at least one dose of Rotarix®.

Race

Race was reported by the study participants' guardian. The other race category included Asian, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, or unknown.

Insurance Status

Public insurance included Medicaid programs. Private insurance included PPO, HMO, and POS programs.

3.4 Statistical Analyses

The rotavirus positive and negative cohorts were established based on laboratory testing of stool samples. Odds ratios and a corresponding 95% CI for the relationship between disease status, vaccine type, number of doses of vaccine received, race, and insurance status and disease severity were calculated for each vaccine group. Similar analyses were conducted based on the number of doses of vaccine received. Univariate regression analysis of disease severity by disease status, vaccine type, number of vaccine doses, race, and insurance status were conducted. Multivariate regression analysis between disease severity and vaccine type while controlling for number of vaccine doses and demographic covariates were conducted as well.

All analyses were conducted using a statistical software package (SPSS 19.0 version for Windows; SPSS Inc., Chicago, IL, USA).

CHAPTER IV:

RESULTS

4.1 Descriptive Statistics

In two separate rotavirus seasons (January-June 2010 and 2011), 660 children who presented with AGE symptoms to one of the three CHOA hospitals' ED or inpatient departments were approached for enrollment into the study. One hundred and eleven guardians of approached patients declined participation. Reasons for refusal included not wanting to participate in research and not wanting to collect stool. Of the 549 children who consented to be in the study, stool samples were collected from 430 of them, and the remaining 119 patients were lost to follow up. Three of the subjects had to be withdrawn from the study. One subject was less than 55 days old. A stool sample was collected more than 14 days after enrollment for another subject. The third subject was a duplicate enrollment. The remaining 427 stool samples were tested for rotavirus, and 119 were found to be rotavirus positive, whereas the other 308 were negative (Figure 1).

More than half of all study participants, 273 (63.9%) had severe disease. In each vaccine type category, majority of participants had severe disease. Ninety-five (77.2%) children who did not receive, 48 (64.0%) children who received RotaTeq®, 73 (56.5%) children who received Rotarix®, 33 (55.9%) children who received mixed vaccine regimens, and 24 (60.0%) children who received at least one dose of an unknown vaccine type all developed severe disease. Similarly, 29 (65.9%) children who received only 1 vaccine dose, 103 (65.9%) children who received 2 doses, and 46 (52.3%) children who received 3 doses of rotavirus vaccine all developed severe disease (Table 2).

119 (27.9%) participants were rotavirus positive and 308 (72.1%) were rotavirus negative. The largest vaccine group was Rotarix®, 130 (30.4%), followed by no vaccine, 123 (28.8%), RotaTeq®, 75 (17.6%), and mixed dosing, 59 (13.8%). 40 (9.4%) participants received at least one unknown type of rotavirus vaccine. Study participants were most likely to receive 2 doses of vaccine 172 (40.3%) or no vaccine 123 (28.8%). Majority of participants were Black, 265 (62.1%) and had public insurance (multiple programs), 330 (72.2%) (Table 1).

There was a significant difference in the likelihood of racial groups to be vaccinated (receive at least one dose of a rotavirus vaccine) (p-value: 0.001). Specifically, Hispanic children were more likely to be vaccinated than White children (OR 2.7, 95% CI: 1.1-6.7). There was no significant difference in the likelihood of Black children to be vaccinated when compared to White children (OR 0.7, 95% CI: 0.4-1.3). No significant differences were observed in the likelihood of children with public and private insurance to be vaccinated (p-value: 0.251).

4.2 Univariate Analyses

Rotavirus positive children were more likely to have severe disease than rotavirus negative children (OR 3.8, 95% CI: 2.2-6.5). Receiving a mixed vaccine regimen had similar protection against severe disease to receiving only RotaTeq® or Rotarix® (Mixed: OR 0.4, 95% CI: 0.2-0.7; RotaTeq®: OR 0.5, 95% CI: 0.3-0.90; Rotarix®: OR 0.4, 95% CI: 0.2-0.7). Receiving one or two doses of vaccine, regardless of type, was protective against severe disease, when compared to children who did not receive vaccine (2 doses: OR 0.6, 95% CI: 0.3-0.9; 3 doses: OR 0.4, 95% CI: 0.2-0.7). Black and Hispanic children were less likely to develop severe disease than White children (Black: OR 0.4, 95% CI 0.2-0.9; Hispanic: OR 0.3, 95% CI: 0.1-0.7). Children with private insurance were also more likely to develop severe disease than those without insurance (OR 3.1, 95% CI 1.2-8.3) (Table 3).

4.3 Multivariate Analyses

When controlling for number of doses and demographic covariates, receiving only RotaTeq® (n=75), only Rotarix® (n=130), or a combination of the two vaccines (n=59) all provided significant protection against severe disease when compared to children who did not receive vaccine (Mixed: OR 0.1, 95% CI: 0.02-0.5; RotaTeq®: OR 0.1, 95% CI: 0.02-0.5; Rotarix®: OR 0.1; 95% CI 0.01-0.3). When controlling for vaccine type and other demographic covariates, only three doses of vaccine offered significant protection against severe disease (OR 0.3, 95% CI: 0.2-0.6). In the multivariate model, Black and Hispanic children persisted in being less likely to develop severe disease than White children (Black: OR 0.4, 95% CI 0.2-0.8; Hispanic: OR 0.3, 95% CI 0.1-0.7). Children with private insurance were 4.0 times more likely to develop severe disease than those with no insurance (95% CI 1.2-12.9) (Table 4).

CHAPTER V:

DISCUSSION AND CONCLUSION

5.1 Discussion

The results of this study of children under three seen in an urban hospital system for diarrhea suggest children who receive a mix of both RotaTeq® and Rotarix® are adequately protected against severe disease, compared to children who do not receive vaccines. That is, children who receive mixed rotavirus vaccine regimens fare similarly to those who only receive RotaTeq® or Rotarix® in terms of protection against severe disease.

Our analysis also revealed that children with private insurance were more likely to develop severe disease than children with no insurance. These findings contradict previous studies which found that the Medicaid population had a disproportionate number of hospitalizations from rotavirus gastroenteritis than other populations.[17-18] Our contradictory findings may be attributed to children with private insurance already seeking medical attention elsewhere before coming to the ED, causing them to be enrolled in the study when their disease had progressed further.

Despite well established racial and insurance-related disparities in rotavirus vaccination and disease, the disparities found in our studies are not consistent with those found in previous literature.[15-18] We found that Black and Hispanic children were actually less likely to develop severe disease than White children. Yen and colleagues also found that White children were more likely to develop rotavirus gastroenteritis prior to the introduction of the rotavirus vaccines but had largely diminished in 2008.[15] Whereas Yen and colleagues' study analyzed national data, the data set used for this study only evaluated children in the metro-Atlanta area. The national

demographic profile differs from that of the metro-Atlanta area, which could account for different results. It is possible that although racial differences in rotavirus vaccination and disease have been largely diminished nationally, they may persist in localized areas.

A previous study of a five year period showed that several children may be excluded from receiving the rotavirus vaccine because they miss the age windows to receive doses.[20] Our findings suggest that availability of a specific rotavirus vaccine should not be a factor in children's failure to receive the rotavirus vaccine. Pediatricians should work to ensure that their patients receive a rotavirus vaccine on the proper schedule. Specifically, a child should receive a rotavirus vaccine on the proper schedule, even if the vaccine available at the time is not the same brand as the one they received previously.

5.2 Limitations of the Study

This study had several limitations. Disease severity was determined using the Vesikari scale. The Vesikari scale is dichotomous and categorizes diarrheal disease as severe or non-severe, which does not give a full understanding of the range of disease severity among study participants. Other scales of diarrheal disease severity categorize disease into more than two categories. These scales also consider factors not included in the Vesikari scale, such as behavioral signs and symptoms, to determine disease severity.[19]

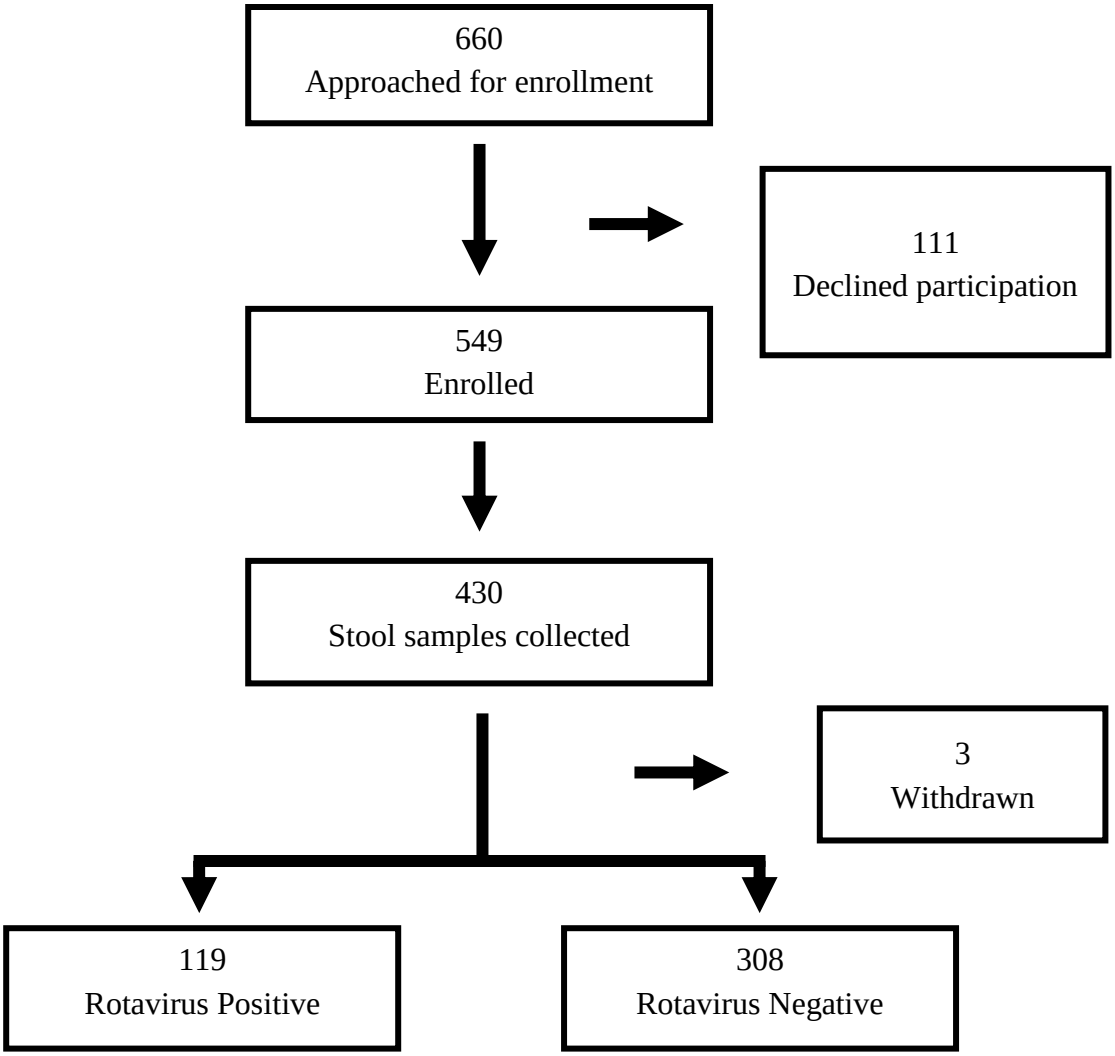
5.3 Recommendations

In the future, it may be helpful to assess disease severity using a different scale. The sample size used for our analysis was relatively small. More studies should be conducted to further evaluate the efficacy of mixed rotavirus vaccine regimens.

5.4 Conclusion

Three doses of rotavirus vaccine, regardless of vaccine type, are protective against severe disease, but one or two doses are not. Receiving a mixed regimen of vaccine is also effective in preventing severe disease. As such, pediatricians should give patients the rotavirus vaccine on schedule, regardless of the type of vaccine. They should also continue to stress the importance of receiving all doses of the rotavirus vaccine. More studies should be done to evaluate the impact and effectiveness of mixed rotavirus vaccine regimens.

Figure 1. Diagram of all patients approached and enrolled in study.



From the 430 patients who stool samples were collected from, 3 were withdrawn from the dataset. (One patient was younger than 55 days, one stool sample was collected more than 14 days after enrollment, and one patient had previously been enrolled in the study). Majority of the patients who declined participation did so because they did not want to participate in research or did not want to collect stool.

Table 1. Descriptive statistics of enrolled subjects (n = 427).

Variables	All		Rotavirus Positive (n=119)	Rotavirus Negative (n=308)
	Sample	p-value		
Severity				
Not severe	154 (36.1%)	<0.0001	20 (16.8%)	134 (43.5%)
Severe	273 (63.9%)		99 (83.2%)	174 (56.5%)
Vaccine Type				
RotaTeq ®	75 (17.6%)	0.0047	15 (12.6%)	60 (19.5%)
Rotatirx ®	130 (30.4%)		23 (19.3%)	107 (34.7%)
Mixed dose	59 (13.8%)		8 (6.7%)	51 (16.6%)
None	123 (28.8%)		65 (55.5%)	58 (18.8%)
Unknown	40 (9.4%)		8 (6.7%)	32 (10.4%)
Vaccine Dose				
0 doses	123 (28.8%)	0.0090	65 (54.6%)	58 (18.8%)
1 dose	44 (10.3%)		10 (8.4%)	34 (11.0%)
2 doses	172 (40.3%)		31 (26.1%)	128 (45.8%)
3 doses	88 (20.6%)		13 (10.9%)	75 (24.4%)
Gender				
Male	244 (57.1%)	0.4153	63 (52.9%)	181 (58.8%)
Female	183 (42.9%)		56 (47.1%)	127 (41.2%)
Age:				
0-2 months	21 (4.9%)	0.2943	5 (4.2%)	16 (5.2%)
3-5 months	75 (17.6%)		12 (10.1%)	63 (20.5%)
6-8 months	91 (21.3%)		19 (16%)	72 (23.4%)
9-11 months	78 (18.3%)		17 (14.3%)	61 (19.8%)
12-23 months	155 (36.3%)		61 (51.3%)	94 (30.5%)
$\geq$ 24 months	7 (1.6%)		5 (4.2%)	2 (0.6%)
Race				
White	59 (13.8%)	0.0266	16 (13.4%)	43 (14%)
Black	265 (62.1%)		81 (68.1%)	184 (59.7%)
Hispanic	80 (18.7%)		14 (11.8%)	66 (21.4%)
Other	23 (5.4%)		8 (6.7%)	15 (4.9%)
Insurance				
Public	330 (72.2%)	0.0206	86 (72.3%)	244 (79.2%)
Private	31 (7.3%)		11 (9.2%)	20 (6.5%)
None	50 (11.7%)		16 (13.4%)	34 (11%)
Unknown	16 (3.7%)		6 (5%)	10 (3.2%)

Disease severity was defined using the Vesikari scale. Participants who received a mixed vaccine dose were defined as those who received at least one dose of RotaTeq® and one dose of Rotarix®. The vaccine dose category represents the number of rotavirus vaccines a patient had received at the time of their illness, regardless of the number of doses received. The other race

category included Asian, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, or unknown. Private insurance included PPO and HMO. Public insurance refers to Medicaid programs.

Table 2. Percentage of vaccine type and dose among subjects with severe disease (n=273).

	Severe Disease	p-value
Vaccine Type		
None	95 (77.2%)	
RotaTeq ®	48 (64.0%)	
Rotarix ®	73 (56.5%)	0.005
Mixed	33 (55.9%)	
Unknown	24 (60.0%)	
Vaccine Doses		
0 doses	95 (77.2%)	
1 dose	29 (65.9%)	0.001
2 doses	103 (60.0%)	
3 doses	46 (52.3%)	

Disease severity was defined using the Vesikari scale. Participants who received a mixed vaccine dose were defined as those who received at least one dose of RotaTeq® and one dose of Rotarix®. The vaccine dose category represents the number of rotavirus vaccines a patient had received at the time of their illness, regardless of the number of doses received.

Table 3. Univariate analysis of disease severity by covariates.

Variables	Severe Disease		
	OR	95% CI	p-value
Disease Status			
Rotavirus Negative	1.00	Referent	
Rotavirus Positive	3.8	2.2-6.4	<0.001
Vaccine Type			
None	1.00	Referent	
RotaTeq ®	0.5	0.4-0.9	0.036
Rotarix ®	0.4	0.2-0.7	<0.001
Mixed	0.4	0.2-0.7	0.003
Vaccine Doses			
0 doses	1.00	Referent	
1 dose	0.6	0.3-1.3	0.216
2 doses	0.6	0.3-0.9	0.024
3 doses	0.4	0.2-0.7	0.001
Race			
White	1.00	Referent	
Black	0.4	0.2-0.9	0.017
Hispanic	0.3	0.1-0.7	0.003
Other	0.5	0.1-1.4	0.176
Insurance			
None	1.00	Referent	
Public	0.7	0.4-1.3	0.0074
Private	3.1	1.2-8.3	0.0856
Unknown	2.6	0.7-9.2	0.3022

Disease severity was defined using the Vesikari scale. Participants who received a mixed vaccine dose were defined as those who received at least one dose of RotaTeq® and one dose of Rotarix®. There were 40 (9.4%) patients who received at least one rotavirus vaccine of an unknown type and were, therefore, not included in the analysis. The vaccine dose category represents the number of rotavirus vaccines a patient had received at the time of their illness, regardless of the number of doses received. The other race category included Asian, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, or unknown. Private insurance included PPO and HMO. Public insurance refers to Medicaid programs.

Table 4. Multivariate analysis of disease severity by covariates.

Variables	Severe Disease		
	OR	95% CI	p-value
Vaccine Type			
None	1.0	Referent	
RotaTeq ®	0.1	0.02-0.5	0.006
Rotarix ®	0.1	0.01-0.3	0.001
Mixed	0.1	0.02-0.5	0.004
Vaccine Doses			
0 doses	1.00	Referent	
1 dose	0.7	0.3-1.5	0.400
2 doses	0.7	0.4-1.1	0.135
3 doses	0.3	0.2-0.6	<0.001
Gender			
Male	1.0	Referent	
Female	0.8	0.5-1.2	0.354
Age			
0-2 months	1.0	Referent	
3-5 months	1.0	0.4-2.8	0.937
6-8 months	1.4	0.5-3.8	0.491
9-11 months	2.0	0.7-5.6	0.168
12-23 months	1.7	0.7-4.5	0.254
24+ months	1.7	0.3-12.0	0.571
Race			
White	1.0	Referent	
Black	0.4	0.2-0.8	0.014
Hispanic	0.3	0.1-0.7	0.006
Other	0.3	0.1-1.1	0.063
Insurance			
None	1.0	Referent	
Public	1.6	0.9-3.1	0.128
Private	4.0	1.2-12.9	0.021
Unknown	3.5	0.9-14.5	0.083

Disease severity was defined using the Vesikari scale. Participants who received a mixed vaccine dose were defined as those who received at least one dose of RotaTeq® and one dose of Rotarix®. There were 40 (9.4%) patients who received at least one rotavirus vaccine of an

unknown type and were, therefore, not included in the analysis. The vaccine dose category represents the number of rotavirus vaccines a patient had received at the time of their illness, regardless of the number of doses received. The other race category included Asian, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, or unknown. Private insurance included PPO and HMO. Public insurance refers to Medicaid programs.

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