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Rotavirus Vaccination Rate Disparities Seen Among Infants with Acute Gastroenteritis (AGE)

Trisha Chan
Georgia State University

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ABSTRACT

TRISHA CHAN

Rotavirus Vaccination Rate Disparities Seen Among Infants with Acute Gastroenteritis (AGE)
(Under the direction of Lisa Casanova, PhD, Faculty Member)

Background: Rotavirus is one of the most common diarrheal diseases in children less than 5 years of age. Rotavirus vaccines have greatly reduced this burden in the United States. An examination was conducted to determine possible disparities in RV vaccination rates compared to DTaP.

Methods: Children were actively enrolled during two rotavirus seasons from January-June of 2010 and 2011 in the Emergency Departments (ED) and inpatient floors from all Children's Healthcare of Atlanta (CHOA) sites (Scottish Rite, Egleston, and Hughes Spalding) with acute gastroenteritis (AGE). Data and a stool sample were collected from enrolled children and samples were tested for presence of rotavirus using an enzyme immunoassay (EIA) kit (Rotaclone). Vaccination records were abstracted from the state immunization registry and primary healthcare providers to examine complete and incomplete vaccination status. This cohort of children with vaccination records were used for this analysis. Cases were identified as children receiving a complete RV dose series and controls were identified as children with incomplete RV doses. A logistic regression model was used to determine disparities seen amongst children with incomplete vaccination status.

Results: Of the 660 patients that were approached for this study, 414 participants were included in this retrospective cohort analysis. 46.9% had incomplete rotavirus vaccination status and were more likely to be positive for rotavirus AGE (OR 1.76, 95% CI 1.46-2.13). Black infants had a higher rate of incomplete RV compared to whites (p-value 0.0006). When controlling for covariates, racial differences were no longer significant (OR 1.37 95% CI 0.77-2.57); however household size (p-value 0.0343), age at onset of illness (p-value 0.0061), and DTaP vaccination status (p-value < 0.0001) were all significant in determining vaccination status for children.

Conclusions: Racial disparities and socioeconomic differences are not evident in determining rotavirus vaccination rates; however, household size, a possible social determinant, has an effect on RV status. In addition, timely vaccinations are important in preventing incomplete RV vaccination status, due to RV vaccine age restrictions.

ROTAVIRUS VACCINATION RATE DISPARITIES SEEN AMONG INFANTS WITH
ACUTE GASTROENTERITIS (AGE)

By

TRISHA CHAN

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By

TRISHA CHAN

Approved:

Lisa Casanova, PhD
Committee Chair

Lilly Immergluck, MD
Committee Member

November 20, 2013
Date

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The author of this thesis is:

Trisha Chan
C/o Institute of Public Health
Georgia State University
P.O. Box 3995
Atlanta, GA 30302-3995

The Chair of the committee for this thesis is:

Lisa Casanova, Ph.D.
Institute of Public Health
Georgia State University
P.O. Box 3995
Atlanta, Georgia 30302-3995

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NAME OF USER	ADDRESS	DATE	TYPE OF USE (EXAMINATION ONLY OR COPYING

Curriculum Vitae

NAME Trisha Chan
trishabchan@gmail.com

EDUCATION

Georgia State University
Atlanta, Georgia 2012-2013
Degree: Masters of Public Health
Area of Concentration: Epidemiology

Georgia State University
Atlanta, Georgia 2007-2010
Post-Baccalaureate
Area of Concentration: pre-medical studies

Georgia Institute of Technology
Atlanta, Georgia 2002-2006
Degree: B.S. in Management/Business
Area of Concentration: Marketing

EXPERIENCE

Senior Research Coordinator 2011-present
Morehouse School of Medicine
Atlanta, Georgia

Research Assistant 2009-2011
Morehouse School of Medicine
Atlanta, Georgia

PUBLICATIONS

1. L Cheng Immergluck, S Khizer, **T Chan**, E Alema-Mensah, RC Jerris, M Farley. Completeness of rotavirus vaccination and its impact on rotavirus disease. *Clin Transl Sci* 2011, 4(2):99.
2. Margaret M. Cortese MD, Lilly Cheng Immergluck MD, Melissa Held MD, Shabnam Jain MD MPH, **Trisha Chan BS**, Alexandra Grizas MPH, Saadia Khizer MD MPHP, Carol Barrett MA, Osbourne Quaye PhD, Slavica Mijatovic-Rustemapasic MSc, Rashi Gautam PhD, Michael Bowen PhD, Jessica Moore MPH, Jacqueline E. Tate PhD, Umesh D. Parashar MBBS MPH, and Marietta Vazquez MD. Effectiveness of Monovalent and Pentavalent Rotavirus Vaccine. *Pediatrics* 2013; 132; (1):e25.
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CHAPTER I:

INTRODUCTION

1.1 Background

Before the inception of rotavirus vaccines, rotavirus remained the leading cause of severe diarrhea in children in the United States (US).¹ Beginning in 2006, two rotavirus vaccines (RV) were licensed for use in the US: Rotarix® (GlaxoSmithKline Biologicals; RV1), a human, live attenuated 2-dose vaccine and RotaTeq® (Merck & Co., Inc.; RV5), a live, oral pentavalent three-dose vaccine. Although national introduction of RV has caused an overall decline in rotavirus gastroenteritis hospitalizations in children of all races, disparities in Black children and children under Medicaid insurance observed in pre-vaccine years in the US still persist in post licensure times.²⁻⁴

An analysis of RV5 during its first six months of availability (August 2006 through January 2007) reported that a significant portion of children analyzed from Pennsylvania's immunization registry were being excluded, due to age, from receiving any RV5 doses and from completing the 3 dose regimen series.⁵ However, a large prospective cohort study conducted in 2009 found that 84.3% of all patients completed a full RV series. More children in the RV1 cohort were fully immunized than in the RV5 cohort, due to either missed dosing or incorrect dose timing (91.0% vs. 83.4%; $p < 0.001$).⁶

Previous studies in the US have reported that children who are under-immunized, with under-immunization defined as those who have received some vaccines but have not completed all of the doses, are more likely to be Black and come from a low socio-economic background than fully immunized children. Conversely, children who are unimmunized, or those who had

parents who refused vaccines, tend to be White and from higher income households.^{7,8}

Identifying disparities that might exist for rotavirus can have major impact on the types of vaccine programs and populations to target. Currently, disparities associated with rotavirus vaccination rates have not been determined or examined in previous literature.

1.2 Purpose of Study

The purpose of this study was to determine if racial, ethnic, socioeconomic status and insurance status disparities exist in completion rates for RV using a retrospective cohort from primary surveillance conducted at Children's Healthcare of Atlanta (CHOA) hospitals.

1.3 Research Question

1. Are previously reported disparities in rotavirus and immunizations, such as race, ethnicity, or insurance status also associated with incomplete RV vaccination status?
2. Are there other socioeconomic factors and disparities associated with incomplete RV vaccination status?

CHAPTER II:

REVIEW OF THE LITERATURE

2.1 Rotavirus Background

Diarrheal diseases have been one of the leading causes of death in children worldwide. Sources of diarrheal illnesses range greatly where most bacterial and parasitic origins come from sanitation and hygiene factors; while infectious agents, tend to originate from modes of transmission between person-to person contact or from person-to-environment.⁹ Before the identification of human rotavirus in 1973, direct infectious causes of diarrheal diseases were difficult to determine. Since this discovery, rotavirus has been estimated to contribute to 40-50% of severe diarrhea worldwide in children less than 5 years of age.¹⁰

Rotavirus is mainly transmitted through person-to-person contact, mainly through the fecal oral route and is difficult to treat with conventional diarrheal therapy, due to a lack of antimicrobial therapy as well as less effective oral rehydration therapies, due to severe vomiting often present in children with rotavirus.¹¹ Clinical signs and symptoms of rotavirus include watery diarrhea, vomiting and/or fever, which lead to loss of fluids that can last up to 2-7 days and potentially lead to dehydration. These symptoms can vary considerably in regards to severity, with the most severe cases occurring in infants with their first infection occurring after 3 months of age.⁹ The severity of disease in these infants is partially due to the fact that rotavirus exhibits natural protection, where neonates are protected using maternal antibodies and adults are protected through acquired immunity.¹²

In many areas in the world, mainly regions with temperate climates, rotavirus exhibits seasonal patterns with peaks of disease occurring in the winter months. During these winter

months, rotavirus has been estimated to be responsible for up to 70% of hospitalizations related to diarrhea.⁹ In the United States, rotavirus season usually begins in the southwest in late fall and peaks in December and January and transitions to the northeast, with the highest rates occurring during March and April.¹³ Introduction of rotavirus vaccinations, though, have led to a shift in the US trend and has shortened as well as delayed the rotavirus season.¹⁴

2.2 Burden of Disease

Rotavirus infection is universal in that the incidence of children under the age of 5 is the same in developed and developing countries with 80-95% of these children suffering at least 1 episode of rotaviral gastroenteritis.^{9,15} Although rotavirus only accounts for 5-10% of total cases of gastroenteritis, it is usually associated with more severe cases. It is estimated that each year there are 114 million episodes of rotaviral gastroenteritis worldwide, with 24 million requiring clinic visits, 2.4 million needing hospitalization, and results in an estimated 400,000-500,000 deaths per year, with most of these deaths occurring in Africa and Asia.^{12,16,17}

In the United States alone and before the implementation of vaccines, rotavirus accounted for 410,000 physician visits, over 200,000 emergency room (ER) visits, 55,000-75,000 hospitalizations in young children, and 20-60 deaths.¹ In 2007, using a cost effectiveness model it was estimated that rotavirus contributed to \$319 million in direct healthcare costs from hospitalizations, clinic visits, and ER visits. Indirect costs, such as parental days lost, were estimated at \$574 million, totally \$893 million in total societal costs.¹⁸

2.3 Vaccine Development

Due to the significant global burden of disease associated with rotavirus, the World Health Organization (WHO) recommended the need for vaccine development. Since rotavirus exhibited protective immunity from repeated infections, this same rationale was used to create a

vaccine. The first vaccine trial began in 1983, investigating the effectiveness of an oral vaccine derived from a bovine strain (RIT 4237). Results demonstrated that live oral vaccines were effective in protecting infants from infection, that protection was greatest against the most severe cases, and animal strains were possible to use against human strains; however, the vaccine failed to show consistent efficacy in multiple countries and development efforts were suspended.^{16,19}

It took 15 more years to license a vaccine and Rotashield® (Wyeth) was introduced in 1998 as a tetravalent rhesus vaccine containing G1-G4 strains. Clinical trials occurred in parts of the US, Finland and Venezuela and demonstrated an 80-100% efficacy in preventing severe diarrhea. The vaccine was recommended for routine use in the US and was given to more than 60,000 infants in the first 9 months; however, in July 1999 Rotashield® was removed, due to reports of a heightened risk of intussusception within the first 2 weeks of the first dose being administered. Although the actual risk remains unclear to this day and accounted for 1 intussusception case out of 10,000 vaccinated, the vaccine remained withdrawn for further use.^{12,16}

Two vaccines were later developed after Rotashield® was taken off the market and provided 2 different approaches to their development. Rotateq® (Merck) used a combination of 5 different bovine human re-assortment strains and is administered in 3 doses at 2, 4 and 6 months of age, not to exceed 8 months.²⁰ Due to the heightened concerns from Rotashield®, the Rotavirus Efficacy and Safety Trial (REST) Study Team recruited more than 60,000 infants to determine efficacy and intussusception rates for Rotateq®. During this trial, 12 occurrence of intussusception occurred in the vaccine group and 15 in the placebo group within 1 year after the first dose. Results demonstrated a vaccine efficacy of 98% against severe gastroenteritis and a

reduction of hospitalizations and ER visits by 94.5%.²¹ From these findings, Rotateq® was licensed in the US in February 2006 and was recommended for routine use in children.¹⁶

The second vaccine, Rotarix® (GlaxoSmithKline), is a human, live attenuated oral vaccine, and is based on the idea of protective immunity. This vaccine is administered in 2 doses and is recommended at 2 and 4 months of age, not to exceed 8 months.²⁰ Rotarix® also went through intense safety and efficacy trials, with over 60,000 infants in 11 Latin American countries and Finland enrolled. Results indicated that this vaccine was 85% effective against rotavirus hospitalizations and 100% effective against severe rotavirus. Intussusception rates were also noted and had 6 cases in the vaccine group and 7 in the placebo. It was concluded from these trials that Rotarix® was efficacious and had no association with increased risk of intussusception.²² This vaccine was first licensed in Mexico and the Dominican Republic in 2004 and was later introduced into 35 countries around Europe and licensed in the US in June 2008.^{16,20}

In May 2010, Rotarix® was temporarily suspended, due to identification of porcine circovirus (PCV1) in the vaccine, even though there was no health risk for humans associated with PCV1.²³ Testing was performed on both vaccines and it was determined that Rotateq® also had traces of PCV1, although suspension was not done on this vaccine. The suspension on Rotarix was later lifted later in the year after no risks were identified.²⁴

2.4 Vaccine Safety and Efficacy

In 2009, WHO recommended that rotavirus vaccines be introduced in all countries worldwide, in particular those countries with a high diarrheal rate of mortality.¹⁷ During this time, multiple studies were being performed to determine the efficacy and safety once Rotateq® and Rotarix® were put into routine immunization programs. Several studies have observed

major declines in hospitalization rates due to rotavirus in high and middle income countries, where vaccines have been introduced.²⁵⁻²⁷

Vaccine efficacy (VE) studies in the US have demonstrated a Rotateq® VE between 89-94%, and a VE against rotavirus gastroenteritis hospitalizations and ER visits of 100%, with a reduced rate of visits occurring between each dose of Rotateq®.^{20,28-30} It has also been seen that 2 doses of Rotateq® seem to provide ample protection, with a 90% VE, although the effectiveness declines to 66% with just 1 dose administered.²⁸ Rotarix® has also shown high efficacy in the US, with a VE of 91% and a reduction of hospitalizations and office visits; however, further studies need to be done in order to understand the full impact of Rotarix® in the US and developing countries.^{9,20}

Developing countries have seen more variability within its VE, with a VE ranging from 39-77%; however, this is a vast improvement compared to the first generation vaccine, Rotashield® that only produced 20% efficacy in developing countries.³¹ In addition, some countries have seen a decline in efficacy after the first year of life. In an El Salvador study, VE was 83% during infancy and fell to 59% for those older than 1 year of age.^{32,33} Although these numbers are lower and more variable than developed countries, there has still been absolute reduction in severe diarrhea disease in countries that have introduced these vaccines.³¹

Intussusception has been a concern for both vaccines and vaccine development clinical trials demonstrated that there was no risk involved with these two vaccines. As more programs adopt these vaccines into routine use, further examination has been done to see if any changes have occurred from the initial trials. There does not seem to be any further risk for intussusception associated with these two vaccines; however, international data suggests a slight risk after the first dose for children 8-11 weeks, but the numbers are still very small and the

benefits outweigh the low risks that are currently present. Further monitoring is essential to ensure that these vaccines are safe and effective globally.³⁴

2.5 Rotavirus Disparities

Studies have been performed pre-licensure and post-licensure of rotavirus vaccines in order to determine if any changes have occurred in regards to disparities, such as race and insurance. Using the largest US hospital database, The Healthcare Cost and Utilization Project (HCUP), hospitalization rates due to rotavirus were examined comparing races. Compared to white children, black infants < 6 months had significantly higher hospitalization rates as well as an increased risk for death.² Yen et al found similar risks concerning black infants. After post-licensure of vaccines, disparities for white, older children dissipated as well as an overall decline in hospitalizations due to diarrhea; however, black infants continued to have higher rates of hospitalizations and ER visits.³⁵ These risks were similar to a study done during 1974-1982, which indicates that disparities with race associated with rotavirus have persisted, despite the implementation of various rotavirus programs throughout the US.^{2,35,36}

Insurance status has also been associated as a disparity with rotavirus disease. Data used from the Kids' Inpatient Database in 2000 and 2003 demonstrated a disproportionate number of Medicaid children being hospitalized for rotavirus compared to non-Medicaid children. Medicaid children accounted for increased hospitalizations, increased length of stay and higher average charges per stay.³ In addition, race and insurance seemed to determine likelihood of patients choosing outpatient care versus ER care, with black children and those with Medicaid utilizing ER visits at almost double the rate of white children.⁴

2.6 Immunization Disparities

Vaccine coverage is important for these rotavirus vaccines, due to the high efficacy seen in both vaccines as well as the possibility for herd immunity. Age restrictions for each vaccine play a major role in the importance of timely vaccinations. These age restrictions have also been found to limit certain children from getting these vaccines. In Philadelphia, it was found that children were more likely to suffer from delayed immunizations, which impacted the ability to get full doses of rotavirus vaccines.⁵ Disparities were also seen in black children in Chicago public schools concerning timely vaccinations. DTaP was used to measure rates and a disproportionate number of black children had low rates of immunizations at 7 months of age. These disparities evened out after 48 months; however, this would not impact rotavirus vaccinations, due to age restrictions enforced for these vaccines.³⁷

Timely vaccinations are of great importance for rotavirus vaccines, due to the age restrictions with each dose. Data is limited in regards to the impact of disparities within rotavirus vaccination rates, due to age restrictions and other possible factors.

CHAPTER III:

METHODOLOGY

3.1 Study Design

This was a retrospective cohort study with data collected from active surveillance conducted during two rotavirus seasons running from January 1, 2010 to June 31, 2010 and January 1, 2011 to June 31, 2011. Pediatric patients who were seen at any of the three CHOA hospital sites, which cover the metro Atlanta area, 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 emergency department (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 ≥ 56 days; and (7) lived in the usual catchment area of the hospital.

Parents of children who met all of the criteria listed above were approached and once an informed consent was obtained, a standardized parent questionnaire was administered, which collected demographic data, medical history of the underlying symptoms, household information, and names and addresses of the child's immunization providers. Rotavirus testing was conducted at the Centers for Disease Control (CDC) using a commercial enzyme immunoassay (EIA) kit (Rotaclone) to categorize children as either rotavirus positive (cases) or rotavirus negative (controls). Immunization records were obtained from immunization providers identified by parents or guardians during enrollment and also from the GA immunization

registry, which is maintained by the department of public health and contains up-to-date immunization records. The study was approved by the institutional review boards at the CDC and CHOA.

3.2 Study Measures

Immunization records were used to determine rotavirus vaccination status. Rotavirus vaccination status was defined as complete or incomplete at the onset of illness. A child was considered to have complete rotavirus vaccination status if they met one of the following criteria: (1) if the child was ≥ 32 weeks at the time of illness and received 3 doses of Rotateq, or 2 doses of Rotarix, or 3 doses of a mix of Rotarix and Rotateq; (2) if the child was ≤ 20 weeks at time of illness and received at least 1 dose of Rotarix; (3) if the child was ≤ 22 weeks at time of illness and had at least 2 doses of Rotateq; (4) if the child was ≤ 12 weeks at time of illness and had at least 1 dose of Rotateq. Children that did not meet the above criteria were considered to have incomplete rotavirus vaccination status. Diphtheria, tetanus and pertussis (DTaP) vaccine was used to compare with rotavirus vaccination status. This vaccine has a similar schedule to Rotateq and a child was considered to have complete DTaP vaccination status if the child had one of the following: (1) at ≤ 12 weeks at time of illness the child had at least 1 dose; (2) at ≤ 22 weeks at time of illness the child had at least 2 doses; (3) at ≥ 32 weeks at time of illness the child had at least 3 doses.³⁸

3.3 Study Definitions

Race

Race was determined from the parent questionnaire done at time of enrollment. The other category included American Indian/Alaskan Native, Asian, and Native Hawaiian/Pacific Islanders or if the parent designated other on the questionnaire.

Insurance Status

Emergency room, inpatient, and clinic records for the day of the visit were used to determine insurance status. Public insurance included Medicaid. Private insurance included PPO, HMO and POS plans. Those that had self-pay were considered to have no insurance.

3.4 Statistical Analyses

Descriptive characteristics of the cohort were done to look at the general characteristics of those used in this analysis, as well as look at the distribution of characteristics for vaccination status. Possible associations between vaccination status and variables were determined by odds ratios and 95% confidence intervals. Variables that were identified as possible covariates included race, ethnicity, insurance status, age at visit, caretaker highest degree level, daycare status, household size and DTaP vaccine status. Multivariable regression analysis was also performed looking at vaccination status and possible covariates. The data analyses was generated using SAS Software, Version 9.2 © 2002-2008 SAS Institute Inc., Cary, NC, USA.

CHAPTER IV:

RESULTS

4.1 Descriptive Statistics

From two rotavirus seasons in January to June of 2010 and 2011, 660 eligible patients were approached at all 3 CHOA hospital sites in the ED and inpatient floors. Of those 660 eligible patients, 111 parents refused participation into the study. Out of the 549 that were successfully enrolled into the study, 430 valid stool samples were collected and tested over the course of each season. Three stools later got withdrawn, due to 1 child being too young for the study, 1 stool sample being collected more than 14 days after illness, and 1 child being enrolled again within 2 weeks of previous enrollment. Of the 427 samples that were used, 422 children were located in the GRITS registry; however, 8 of those children's rotavirus vaccination status could not be determined to be complete or incomplete and were taken out of the analysis. Overall, 414 children were included in this retrospective cohort analysis, with 220 children having complete rotavirus vaccination status and 194 having incomplete status (Figure 1).

Most children were enrolled from the hospital ED 82.4% (341/414) and were not admitted for their AGE illness. The majority of participants were Black 64.6% (257/414), non-Hispanic 81.3% (335/414), rotavirus negative 72.0% (298/414), more than 8 months of age 62.8% (260/414), male 57.2% (237/414) and had public insurance 77.5% (321/414).

Almost half of the study participants had incomplete rotavirus vaccination status (46.9%) at the time that they presented to the hospital with AGE symptoms. Of those that were incomplete, the majority of children, 73.4% (138/194), identified themselves as black and non-Hispanic (89.6%, 173/194). More than 40% of children with incomplete status were positive for

rotavirus compared to only 16.8% positive for children with complete status (OR 1.76, 95% CI 1.46-2.13). In addition, children with incomplete vaccination status seemed to have a higher severity of disease with a higher percentage of children being admitted into the hospital and staying between 1-5 days in the hospital compared to complete rotavirus vaccination status children (Table 1).

There were significant differences noted in the distribution of the age at the time of illness, household size, and DTaP vaccination status when comparing incomplete vaccination children to complete vaccination status children. 74.2% (144/194) of incomplete vaccine children were > 8 months of age, while a more even distribution was evident for complete vaccine children, with 52.7% of > 8 months or older children being complete. In addition, children that were > 8 months of age were more likely to be positive for rotavirus AGE (OR 1.49, 95% CI 1.05-2.11, p-value 0.0216). Incomplete rotavirus vaccination children also had a higher proportion of having more than 6 members in their household compared to complete vaccine children (13.9% vs. 5.9%, p-value 0.022). Lastly, 53.1% (103/194) of incomplete vaccine children were incomplete for DTaP vaccine compared to only 9.5% of complete children being incomplete for DTaP vaccine.

4.2 Univariate Analysis

Possible covariates were examined for incomplete RV vaccination status. Children with incomplete vaccination status were more likely to be Black compared to complete vaccine status children (OR 1.61, 95% CI 1.19-2.18). Those that were Hispanic had a protective effect in regards to vaccination status (OR 0.50, 95% CI 0.34-0.74) and were more likely to have complete status. Children that were not in daycare also had a protective effect for vaccination status similar to that found in Hispanics (OR 0.78, 95% CI 0.64-0.95). Household size had a

significant difference between those that reported more than 6 members in the household compared to 3 or less household members (OR 1.50, 95% CI 1.15-1.94). Children that were > 8 months of age were also more likely to have incomplete vaccine status compared to children <= 8 months (OR 1.71, 95% CI 1.33-2.20). Being incomplete for DTaP vaccine also increased a child's likelihood that they would be incomplete for rotavirus vaccine (OR 2.65, 95% CI 2.19-3.19) (Table 2).

4.3 Multivariable Analysis

Multivariable logistic regression analysis was performed to measure if any possible covariates identified in the univariate analysis were possible predictors for incomplete RV vaccination status. Race and ethnicity no longer were significant in determining incomplete vaccination status (Black: OR 1.37, 95% CI 0.77-2.57; Hispanic: OR 0.45, 95% CI 0.19-1.05). Children that were > 8 months of age remained significant and were almost 2 times more likely to have incomplete RV vaccination status in this cohort (95% CI 1.22-3.27). In addition, parents that reported a child's household size > 6 were 2.68 times more likely to be incomplete for RV vaccine status (95% CI 1.08-6.69). DTaP vaccine status was also significant in predicting RV vaccine completion status (OR 7.79, 95% CI 4.47-13.58).

CHAPTER V:

DISCUSSION AND CONCLUSIONS

5.1 Discussion

Previous studies have confirmed that RV1 and RV5 vaccines are both effective in deterring rotavirus disease and sustaining protection in the first 2 years of life; however, the vaccine effectiveness decreases for RV5 with two doses and one dose or an incomplete vaccination status.^{20,28,30,39} This retrospective cohort study confirms the previous studies' analysis for rotavirus vaccine effectiveness in that children with complete vaccination status were less likely to be positive for rotavirus compared to those with incomplete status at onset of AGE illness. Incomplete rotavirus vaccine children also seemed to have higher severity in their illness.

Through this analysis, disparities associated with rotavirus disease and other immunizations that have been evident in earlier studies, specifically race and insurance status, were not apparent^{2,37}. Although racial disparities were seen in the univariate analysis, controlling for other covariates in the multivariable analysis showed non-significant association between race and vaccination status. These findings might suggest that racial disparities associated with immunizations might be diminishing; however, this study only examined children covering a small part of GA, mainly the metro Atlanta area, and might not be reflective to other areas in the US. Insurance status was never found to have a significant association to vaccination status, but these results could have been limited, due to the small number of children reporting private insurance and the majority of children reporting public insurance. A larger

sample is needed to fully understand the relationship between socioeconomic and vaccination status.

The rotavirus vaccines have a unique age restriction compared to other recommended vaccines for routine use. Few vaccines have an upper age limit of such a short time span as the RV vaccines, which might affect children from receiving a full dose of rotavirus vaccine. Secondly, RV vaccines are the only vaccines that are recommended with age limits counted in weeks. This might cause confusion for providers as well as put more stringent age restrictions on rotavirus vaccines compared to other vaccines.⁵ Since these two vaccines have two different dosing schedules, Rotateq® might seem more difficult to achieve complete vaccination status, which has been noted in a large prospective cohort study.⁶ This analysis showed similar issues in regard to complete vaccination status. The comparison for ages was between children less than 8 months of age to those that were greater than 8 months of age. This comparison was used, due to the age limits set by the Advisory Committee on Immunization Practices (ACIP) and American Academy of Pediatrics (AAP).³⁸ The age at onset of illness affected the likelihood of a child having complete vaccination status, which seems to signify the importance for timely vaccinations.

Other vaccines, such as DTaP, seem to be a predictor in determining if a child will receive the rotavirus vaccine. Although children that are incomplete with the DTaP vaccine are 7 times more likely to not receive the rotavirus vaccine, further analysis needs to be done to determine why 46.9% of children that were complete for DTaP were incomplete for rotavirus vaccine. The age of visit might play a role into why there were a high number of children that were incomplete for rotavirus vaccine, but complete for the other DTaP vaccine, since DTaP has fewer restrictions on age for the third dose.

Household size also had an association to determining vaccination status and could possibly serve as a proxy for household crowding. From the analysis, household crowding could possibly play a role in determination of vaccination status. Previous studies have not looked at social determinants related to rotavirus vaccinations and this may be a catalyst in looking at this and possibly other determinants that might affect a child's likelihood of getting vaccinations.

5.2 Limitations of the Study

There were several limitations to this retrospective cohort study. Since this dataset was originally used to examine the vaccine effectiveness of RV1 and RV5, some questions that could have facilitated the analysis were not asked. Therefore, reasons for why certain risk factors exist or do not exist were more difficult to examine. Household size was used as a proxy for household crowding and might not truly reflect crowding. In addition, risk factors that remained significant: age at onset of illness, household size, and DTaP vaccine status had somewhat larger confidence intervals, which indicates that there might be variability within our study cohort.

This analysis only included a cohort of children that covered the metro Atlanta area and might not reflect other populations outside of metro Atlanta or nationally. The catchment area was primarily children with public insurance and Blacks, which might have made it difficult to determine associations with vaccination status. Disparities not shown in this analysis might still persist in other parts of the country. Further analysis needs to be performed to include a larger sample size.

5.3 Recommendations

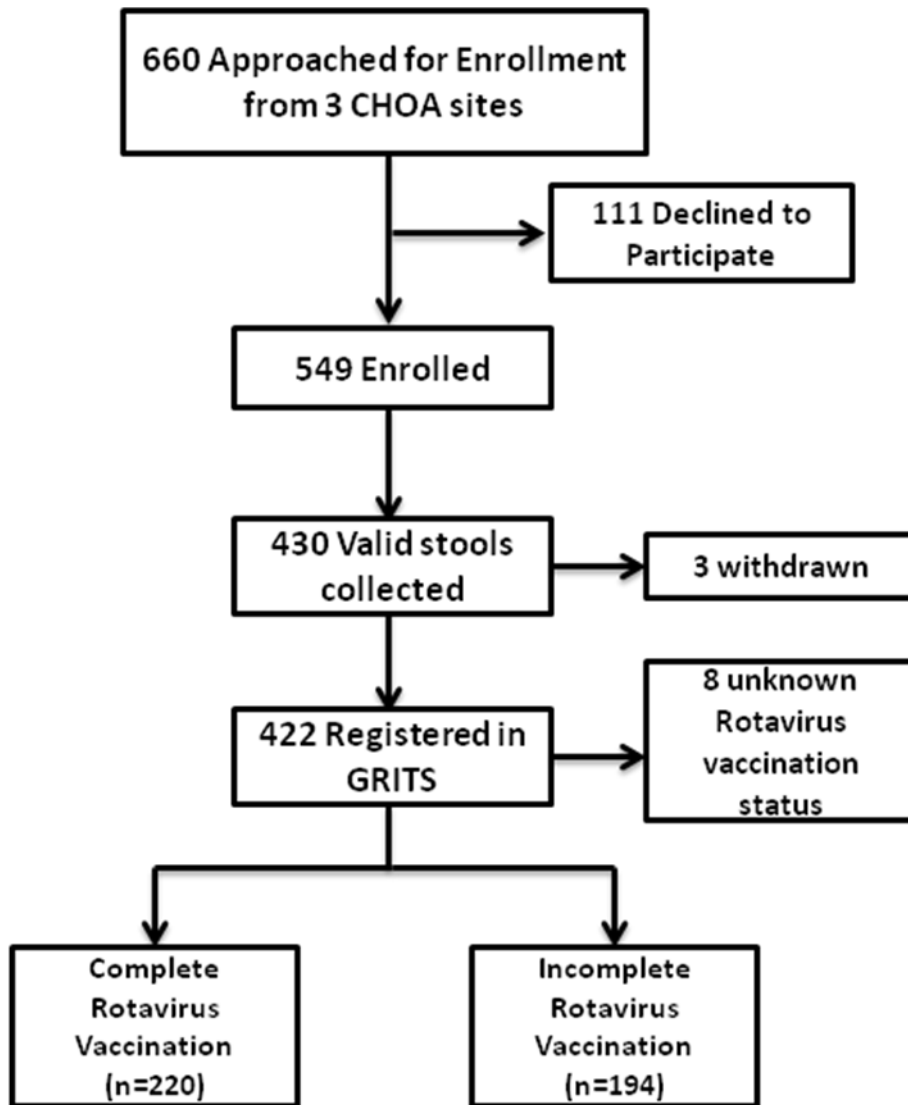
Although racial disparities and insurance were not associated with incomplete vaccination status in this cohort study, other risk factors were identified. It may be beneficial to analyze additional social determinants, such as access to care, to possibly establish target

populations. In addition, pediatricians should stress to parents the importance of timely vaccinations, particularly for RV vaccines, due to its strict age limits.

5.4 Conclusions

RV vaccines have proven to be effective vaccines for combating severe rotavirus disease. It has been shown that these vaccines have continued protection for children in the first two years of life; however, complete vaccinations are imperative in order for these vaccines to sustain its efficacy. Due to age restrictions of these RV vaccines, timely vaccinations are important to complete these vaccines. Advisory committees should examine possibly looking at efficacy for children that are given the RV vaccine after 8 months of age and adjusting the age to include a wider age range. Routine recommended vaccines, specifically DTaP, are associated with determining RV vaccine status, which reinforces the need for timely vaccinations. Certain disparities, such as race and insurance, were originally thought to be associated with incomplete vaccination status were shown as not being significant; however, other social determinants, age and household size, seem to play a role in vaccination status and more studies should be done to examine these and other social determinants and its effect on immunization status.

Figure 1. Enrollment Flow Diagram



Three stool samples were later withdrawn from the dataset (One patient younger than 56 days, one stool sample collected > 14 days after start of illness, and one patient re-enrolled within 14 days of previous enrollment).

Table 1. Descriptive Characteristics (n=414)

Variable	Total Number N=414 (%)	Rotavirus Vaccine Doses		P Value
		Complete N=220 (%)	Incomplete N=194 (%)	
Race^{a,b}				
White	99 (24.9)	66 (31.4)	33 (17.6)	0.0017
Black	257 (64.6)	119 (56.7)	138 (73.4)	
Other	42 (10.6)	25 (11.9)	17 (9.0)	
Ethnicity^c				
Hispanic	77 (18.7)	57 (26.0)	20 (10.4)	<0.0001
Non-Hispanic	335 (81.3)	162 (74.0)	173 (89.6)	
Sex				
Male	237 (57.2)	130 (59.1)	107 (55.2)	0.419
Female	177 (42.8)	90 (40.9)	87 (44.8)	
Rotavirus Cases				
Positive	116 (28.0)	37 (16.8)	79 (40.7)	<0.0001
Negative	298 (72.0)	183 (83.2)	115 (59.3)	
Age at Visit				
Median (IQR)	11.1 (6.3-14.5)	8.2 (5.4-12.1)	12.1 (7.8-18.0)	<0.0001
<= 3months	22 (5.3)	9 (4.1)	13 (6.7)	<0.0001
3-6 months	74 (17.9)	57 (25.9)	17 (8.8)	
6-8 months	58 (14.0)	38 (17.3)	20 (10.3)	
>8 months	260 (62.8)	116 (52.7)	144 (74.2)	
Hospital Duration				
Not Admitted	344 (83.1)	196 (89.1)	148 (76.3)	0.002
1 - 5 days	62 (15.0)	20 (9.1)	42 (21.6)	
> 5 days	8 (1.9)	4 (1.8)	4 (2.1)	
Days of Diarrhea				
Median (IQR)	3.0 (2.0 – 4.0)	3.9 (2.0 – 4.0)	3.0 (2.0 – 5.0)	0.139
<=3	246 (59.4)	138 (62.7)	108 (55.7)	0.299
4-6	130 (31.4)	62 (28.2)	68 (35.1)	
>6	38 (9.2)	20 (9.1)	18 (9.3)	
Billing Category				
ED Only	341 (82.4)	194 (88.2)	147 (75.8)	0.003
Hospital Admission	60 (14.5)	21 (9.5)	39 (20.1)	
Short Stay	9 (2.2)	2 (0.9)	7 (3.6)	
Clinic	4 (1.0)	3 (1.4)	1 (0.5)	
Insurance Status^d				
None	47 (11.8)	28 (13.0)	19 (10.4)	0.5329
Private	30 (7.5)	18 (8.4)	12 (6.6)	

Public	321 (77.5)	169 (78.6)	152 (83.1)	
Diarrhea Episode				
Median (IQR)	6.0 (4.0 – 10.0)	6.0 (4.0 – 9.0)	6.0 (4.0 – 10.0)	0.173
<=3	60 (14.5)	43 (19.5)	17 (8.8)	
4-6	174 (42.0)	85 (38.6)	89 (45.9)	0.007
>6	180 (43.5)	92 (41.8)	88 (45.4)	
DTaP Vaccine				
Complete	290 (70.0)	199 (90.5)	91 (46.9)	
Incomplete	124 (30.0)	21 (9.5)	103 (53.1)	<0.0001
Breastfed^e				
No	124 (30.0)	60 (27.3)	64 (33.0)	
Yes	285 (68.8)	156 (70.9)	129 (66.5)	0.382
Household Size				
Median (IQR)	3.0 (2.0 – 5.0)	3.0 (2.0 – 5.0)	4.0 (2.0 – 5.0)	0.465
<=3	213 (51.4)	117 (53.2)	96 (49.5)	
4-6	161 (38.9)	90 (40.9)	71 (36.6)	0.022
>6	40 (9.7)	13 (5.9)	27 (13.9)	
Attend Daycare				
No	278 (67.1)	159 (72.3)	119 (61.3)	
Yes	136 (32.9)	61 (27.7)	75 (38.7)	0.020
Caretaker Degree^f				
None	100 (24.7)	60 (28.2)	40 (20.8)	
High School/GED	214 (52.8)	107 (50.2)	107 (55.7)	0.399
College	62 (15.3)	31 (14.6)	31 (16.2)	
Graduate	29 (7.2)	15 (7.0)	14 (7.3)	

^a 16 children did not claim a race or race was unknown.

^b Other category included Asian, Multi-Racial, American Indian/Alaskan Native, and Native Hawaiian/Pacific Islander

^c 2 children did not claim an ethnicity or ethnicity was unknown

^d 16 children had unknown insurance status; Public insurance includes children with Medicaid insurance

^e 5 children had unknown breastfeeding status

^f 9 children's caretakers had unknown caretaker degree status

Table 2. Univariate Analysis of Incomplete RV Vaccination Status

Variables	Incomplete Status		
	Odds Ratio	95% CI	p-value
Race			
White	1.00	Referent	
Black	1.61	(1.19-2.18)	0.0006
Other	1.21	(0.77-1.92)	0.4175
Ethnicity			
Non-Hispanic	1.00	Referent	
Hispanic	0.50	(0.34-0.74)	<0.0001
Insurance Status			
Private	1.00	Referent	
Public	1.18	(0.75-1.86)	0.4402
None	1.01	(0.58-1.77)	0.9704
Caretaker Degree			
None	1.00	Referent	
High School/GED	1.25	(0.95-1.65)	0.0980
College	1.25	(0.88-1.77)	0.2125
Graduate	1.21	(0.77-1.89)	0.4264
Daycare			
Yes	1.00	Referent	
No	0.78	(0.64-0.95)	0.020
Age at Visit			
<= 8 months	1.00	Referent	
> 8 months	1.71	(1.33-2.20)	<0.0001
Household Size			
<=3	1.00	Referent	
4-6	0.98	(0.78-1.23)	0.8516
>6	1.50	(1.15-1.94)	0.0092
DTaP Vaccine			
Complete	1.00	Referent	
Incomplete	2.65	(2.19-3.19)	<0.0001

Table. 3 Multivariable Analysis of the relationship between Vaccination Status and risk factors

Risk Factor	Incomplete Status		
	Odds Ratio	95% CI	p-value
Race			
White	1.00	Referent	
Black	1.37	(0.77-2.57)	0.4049
Other	1.11	(0.46-2.71)	0.9023
Ethnicity			
Non-Hispanic	1.00	Referent	
Hispanic	0.45	(0.19-1.05)	0.0640
Daycare			
Yes	1.00	Referent	
No	0.83	(0.50-1.37)	0.4627
Age at Visit			
<= 8 months	1.00	Referent	
> 8 months	1.99	(1.22-3.27)	0.0061
Household Size			
<=3	1.00	Referent	
4-6	1.10	(0.67-1.81)	0.7135
>6	2.68	(1.08-6.69)	0.0343
DTaP Vaccine			
Complete	1.00	Referent	
Incomplete	7.79	(4.47-13.58)	<0.0001

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