THE ROTAVIRUS VACCINE IN A MEDICAID POPULATION:

SERIES COMPLETION AND HEALTH CARE UTILIZATION

by

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ABSTRACT

Coverage estimates for the complete rotavirus vaccine series are considerably lower than the *Healthy People 2020* target, as well as for other vaccinations routinely recommended in early childhood. Regardless, routine rotavirus vaccination in infants has been extremely effective in reducing rotavirus-associated illness in the United States. There are racial and socioeconomic disparities in rotavirus vaccine coverage, as well as lower rates of coverage among rural children. Furthermore, there is evidence of disproportionate disease burden among Medicaid-enrolled children.

Further reductions in rotavirus disease burden are possible with improvements in coverage rates, although coverage may not reflect the full of the impact of rotavirus vaccination. Both the receipt of the complete rotavirus vaccine series, as well as receipt of a partial series, have been shown effective in the prevention of severe illness. Therefore, the present study was conducted within a Medicaid-enrolled population to 1) Examine the association between rural residence and rotavirus vaccination 2) Examine demographic and provider characteristics as potential predictors of rotavirus vaccine series initiation and completion, and 3) Examine differences in rotavirus-associated health care utilization by the status of rotavirus vaccine series completion.

The study population included 293,458 children enrolled in Medicaid between 2010-2017. Nearly 77% of infants received at least one rotavirus vaccine dose; however, only 56% completed the full series. Infants who resided in rural areas were more likely to initiate the vaccine series, but rurality of residence had mixed impact on series completion. The receipt of ≥1 dose of the diphtheria, tetanus, and pertussis (DTaP) vaccine was strongly associated with

rotavirus vaccine series initiation. The strongest predictors of series completion were the receipt of all age appropriate doses of DTaP and receipt of the Rotarix® (RV1) (GlaxoSmithKline Biologicals) vaccine. Analysis of health care utilization found that receipt of any dose of rotavirus vaccine was effective in the prevention of severe illness; however, completion of the series maximized protection against severe cases of rotavirus-associated illness.

DEDICATION

To my best girl, Autumn Jane. You are the sunshine in my day and the greatest gift in my life. You have made me stronger, better, and more fulfilled than I ever imagined possible. I love you big.

To my wonderful husband and best friend, Shawn. Thank you for the sacrifices you made to help me achieve this dream. Thank you for your support, encouragement, and love. I could not have done it without you. I love you.

To my amazing parents, Randy and Nancy Jane Henderson, who have always encouraged me to work hard and dream big. Thank you for your faith, support, love, and countless trips to Alabama. I love you both.

LIST OF ABBREVIATIONS AND SYMBOLS

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
AGE	Acute gastroenteritis
AHRQ	Agency for Healthcare Research and Quality
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CPT	Current procedural terminology
DTaP	Diphtheria, tetanus, and pertussis
ED	Emergency department
ER	Emergency room
hep A	Hepatitis A
hep B	Hepatitis B
Hib	*Haemophilus influenzae* type b
ICD-9	International Classification of Diseases, Ninth Edition
ICD-10	International Classification of Diseases, Tenth Edition
IID	Immunization and infectious disease
IPV	Inactivated poliovirus
IRR	Incidence rate ratio

MMR	Measles-mumps-rubella
MSA	Metropolitan statistical area
NIS	National Immunization Survey
NREVSS	National Respiratory and Enteric Virus Surveillance System
NVSN	New Vaccine Surveillance Network
PCV	Pneumococcal conjugate vaccine
REST	Rotavirus Efficacy and Safety Trial
RR	Relative risk
RUCA	Rural urban commuting area
RV	Rotavirus
RV1	Rotarix®
RV5	RotaTeq®
RVGE	Rotavirus gastroenteritis
VAR	Varicella
VPD	Vaccine preventable disease

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INTRODUCTION

Between 1900 and 2000, life expectancy in the United States increased by 62%, which meant an increase from 47.3 to 76.8 years of life, respectively (National Center for Health Statistics, 2011). By 2014, life expectancy at birth had further increased to 78.8 years (National Center for Health Statistics, 2016). These increases have been due, in large part, to a substantial decrease in childhood mortality (United States Department of Health and Human Services, 2000). Historically, infectious diseases were the major cases of childhood morbidity and mortality in the United States. Childhood mortality due to infectious disease decreased from 61.6% in 1900 to 2.0% by the end of the 20th century, and vaccination is credited with dramatic reduction in both pediatric morbidity and mortality (Baker & Katz, 2004; Guyer, Freedman, Strobino, & Sondik, 2000; US Department of Health and Human Services, 2000). In fact, vaccines are counted among the most beneficial public health achievements in the United States (Centers for Disease Control and Prevention, 2011b). Analysis of the reduction in morbidity and mortality after implementation of national vaccine recommendations found a 92-100% reduction in morbidity and 99-100% reduction in mortality for 10 vaccine preventable diseases with vaccines licensed prior to 1980 (Roush, Murphy, & Group, 2007).

Furthermore, vaccines are considered extremely cost-effective preventive health care (United States Department of Health and Human Services, 2000). Economic evaluation of the childhood immunization program in the United States found that, in direct and total societal costs among the 2009 birth cohort, routine childhood immunization will save $13.5 billion and $68.8

billion through the prevention of 42,000 deaths and 20 million cases of vaccine preventable disease (VPD). Consequently, the analysis found that for each dollar spent on the administration of vaccines during 2009, $3 in direct and $10 in societal costs were saved (Zhou et al., 2014). A separate analysis estimated that routine childhood immunization of children born between 1994-2013 will prevent 732,000 early deaths, 21 million hospitalizations, and 322 million cases of disease, which would save $295 billion in direct and $1.38 trillion in total societal costs (Whitney et al., 2014). Much of the substantial reduction in morbidity, mortality, and costs associated with VPD is attributed to high vaccine coverage levels among infants and children, which reflects the success of the childhood immunization program in the United States (Roush et al., 2007).

Among the most recent additions to the routinely administered vaccinations in young children, coverage estimates for the rotavirus (RV) vaccine is reported to be well below *Healthy People 2020* targets. Worldwide, rotaviruses infect nearly all children by the age of 3-5 years and are the leading cause of severe diarrhea or gastroenteritis in children under age five (Centers for Disease Control and Prevention, 2015a; World Health Organization, 2013). Prior to vaccine implementation in the United States, rotavirus was responsible for 20-60 deaths and an estimated three million infections annually (Centers for Disease Control and Prevention, 2015a; Cortese & Parashar, 2009; Fischer et al., 2007; Glass et al., 1996; Kilgore, Holman, Clarke, & Glass, 1995; Widdowson et al., 2007). Furthermore, studies indicate that RV vaccine coverage is well below that for other routine childhood vaccinations recommended during the same age ranges (Hull, Menzies, Macartney, & McIntyre, 2013; Tate, Cortese, Payne, Curns, Yen, Esposito, Cortes, Lopman, Patel, Gentsch, et al., 2011).

Recommendations of the Advisory Committee on Immunization Practices

The annual recommended immunization schedule for children is determined by the Centers for Disease Control and Prevention (CDC) and is based on recommendations made by the Advisory Committee on Immunization Practices (ACIP) (Centers for Disease Control and Prevention, 2017b). The ACIP is a group of 15 experts in medicine and public health that provides annual vaccine recommendations which include age ranges for vaccine doses, number of and intervals between doses, and contraindications for vaccines (Centers for Disease Control and Prevention, 2012a). The resulting vaccination schedule is approved by the ACIP, the American Academy of Pediatrics (AAP), the American College of Obstetricians and Gynecologists (ACOG), and the American Academy of Family Physicians (AAFP) (Robinson, Romero, Kempe, & Pellegrini, 2017). Vaccination of young children helps to build immunity before infants and young children are exposed to potentially harmful or deadly VPDs (Centers for Disease Control and Prevention, 2013a). The *Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger-United States, 2018* includes dosing schedules, precautions, and contraindications recommended vaccines, including the vaccines for 14 VPDs recommended for children by age 23 months (Centers for Disease Control and Prevention, 2017b). Prior to the age of two, children in the United States are recommended to receive three doses of hepatitis B (hep B), two-three doses of rotavirus (RV), four doses of diphtheria, tetanus, and pertussis (DTaP), three-four doses of *Haemophilus influenzae* type b (Hib), four doses of Pneumococcal conjugate (PCV), three doses of inactivated poliovirus (IPV), one-two doses of influenza, one doses of measles, mumps, rubella (MMR), one dose of varicella (VAR), and two doses of hepatitis A (hep A) vaccines (Centers for Disease Control and Prevention, 2017b).

Immunization and Infectious Disease Objectives in Healthy People 2020

Immunization and infectious diseases are among the topics addressed by *Healthy People 2020*, a document produced for the past three decades that provides an outline for improving health in the United States. Specifically, Immunization and Infectious Disease (IID) Objective 7 addresses coverage levels of vaccines recommended for young children. Table 1 provides a description of vaccine-specific objectives targeted towards children by ages 19 to 35 months (United States Department of Health and Human Services, 2000). Targets within Immunization and Infectious Diseases Objective 7 are set at 90, 85, and 80% coverage of all children in the United States ages 19 to 35 months. A coverage level of 90% allows for consistent control over VPDs and maintenance of heard immunity, the protection of a population that is provided immune individuals (Fine, 1993). Targets for hepatitis A and hepatitis B are set at 85%, a target deemed achievable by vaccines with low rates of coverage at baseline (United States Department of Health and Human Services). The rotavirus vaccine was first recommended in 2006, making the vaccine series one of the most recent additions to the ACIP recommendations for routine immunization in young children. Furthermore, the dosing schedule for the rotavirus series does not allow for catch up doses. As a result, the 2020 target for rotavirus vaccine coverage in the United States was set at 80% (United States Department of Health and Human Services).

Table 1

Healthy People 2020: *Immunization and Infectious Diseases Objective 7*

Objective	Description	Baseline (%)	Target (%)
IID-7.1	Maintain an effective vaccination coverage level of 4 doses of the diphtheria-tetanus-acellular pertussis (DTaP) vaccine among children by age 19 to 35 months	82.5	90.0
IID-7.2	Achieve and maintain an effective vaccination coverage level of 3 or 4 doses of *Haemophilus influenzae* type b (Hib) vaccine among children by age 19 to 35 months	80.9	90.0
IID-7.3	Maintain an effective vaccination coverage level of 3 doses of hepatitis B (hep B) vaccine among children by age 19 to 35 months	89.7	90.0
IID-7.4	Maintain an effective coverage level of 1 dose of measles-mumps-rubella (MMR) vaccine among children by age 19 to 35 months	90.8	90.0
IID-7.5	Maintain an effective coverage level of 3 doses of polio vaccine among children by age 19 to 35 months	92.8	90.0
IID-7.6	Maintain an effective coverage level of 1 dose of varicella vaccine among children by age 19 to 35 months	90.2	90.0
IID-7.7	Achieve and maintain an effective coverage level of 4 doses of pneumococcal conjugate vaccine (PCV) among children by age 19 to 35 months	81.9	90.0
IID-7.8	Achieve and maintain an effective coverage level of 2 doses of hepatitis A vaccine among children by age 19 to 35 months	53.0	85.0
IID-7.9	Achieve and maintain an effective coverage level of a birth dose of hepatitis B vaccine (by annual birth cohort)	70.6	85.0
IID-7.10	Achieve and maintain an effective coverage level of 2 or more or 3 or more doses of rotavirus vaccine among children by age 19 to 35 months	68.6	80.0

Note. Adapted from "Healthy People 2020" by The United States Department of Health and Human Services, Office of Disease Prevention and Health Promotion, 2000. Baseline percentages from 2012, except baseline for IID-7.9 (2005 birth cohort).

Vaccination Coverage in Children

Vaccination coverage rates are an indicator of primary health care in children (Dombkowski, Lantz, & Freed, 2002). Coverage is measured as up-to-date or the proportion of children who have received all age-appropriate vaccine doses (Dombkowski et al., 2002; Rodewald et al., 1999). The National Immunization Survey (NIS) provides estimates of coverage levels of ACIP-recommended vaccines among children in the United States. Analysis of NIS data is utilized to evaluate progress towards Healthy People 2020 goals, as well as to identify groups of children at-risk for VPD, inform program and policy decisions, and evaluate programs designed to increase vaccine coverage among children (Centers for Disease Control and Prevention, 2016a; Luman, Shaw, & Stokley, 2008). Using household interviews selected via random-digit-dialing and provider validated vaccination histories, the NIS uses a large sample size weighted to provide national, regional, state, and local area vaccine coverage estimates (Centers for Disease Control and Prevention, 2016a; Shefer, Santoli, & Singleton, 2007). The size of the nationally representative sample also allows for coverage estimation by demographic factors such as levels of urbanicity, income, race/ethnicity, and gender (Centers for Disease Control and Prevention, 2016a). When coverage estimates are linked to surveillance data, researchers can evaluate the ability of vaccination to prevent disease. The NIS is designed to assess dose counts and cannot evaluate other aspects of the ACIP recommendations or provide small area estimates of coverage outside selected areas (Shefer et al., 2007).

For 2015, national coverage estimates indicate that, among children 19 to 35 months, over 90% of children had received ≥3 doses of hep B, ≥3 doses of IPV, ≥1 dose of MMR, and ≥1 dose of VAR. However, coverage estimates for ≥4 doses of DTaP, ≥4 doses of PCV, and ≥3 or ≥4 doses of Hib (full series) were below the Healthy People 2020 target of 90%. In addition,

coverage estimates for ≥2 doses of hep A and the birth dose of hep B were below the 85% target. Rotavirus vaccination coverage, which can be ≥2 or ≥3 doses dependent upon product, was also well below the target of 80% (Hill, 2016). National coverage estimates for 2010-2016 are provided in Table 2 (Centers for Disease Control and Prevention, 2011a, 2012b, 2013b, 2014, 2015b, 2016b, 2017a). In 2013, there was a statistically significant increase in the coverage of the birth dose of hepatitis B and the rotavirus vaccines (Elam-Evans et al., 2014). Between 2013 and 2014, there was a statistically significant increase in the coverage of the hepatitis A vaccine (Hill, Elam-Evans, Yankey, Singleton, & Kolasa, 2015). In 2015, there were no statistically significant changes in coverage as compared to 2014 (Hill, 2016). National coverage estimates for 2010-2015 reveal that coverage for rotavirus, DTaP, Hib, PCV, hep A, and birth dose of hep B is consistently lower than *Healthy People 2020* targets.

Table 2

Vaccine Coverage Estimates of Children Aged 19 to 35 months United States, 2010-2016 (%)

Vaccine	Doses	Target	2010	2011	2012	2013	2014	2015	2016
Hep B	≥3	90.0	91.8	91.1	89.7	90.8	91.6	92.6	90.5
RV	≥2/3	80.0	59.2	67.3	68.6	72.6	71.7	73.2	74.1
DTaP	≥4	90.0	84.4	84.6	82.5	83.1	84.2	84.6	83.4
Hib (Full Series)	≥3/4	90.0	66.8	80.4	80.9	82.0	82.0	82.7	81.8
PCV	≥4	90.0	83.3	84.4	81.9	82.0	82.9	84.1	81.8
IPV	≥3	90.0	93.3	93.9	92.8	92.7	93.3	93.7	91.9
MMR	≥1	90.0	91.5	91.6	90.8	91.9	91.5	91.9	91.1
VAR	≥1	90.0	90.4	90.8	90.2	91.2	91.0	91.8	90.6
Hep A	≥2	85.0	49.7	52.2	53.0	54.7	57.5	59.6	60.6
Hep B (Birth Dose)	1	85.0	64.1	68.6	71.6	74.2	72.4	72.4	71.1

Note. Data from (Centers for Disease Control and Prevention, 2011a, 2012b, 2013b, 2014, 2015b; Hill, 2016). Targets from *Healthy People 2020*.

Although routine childhood vaccination has proven to be an effective public health strategy, vaccine-preventable diseases have not been eliminated as a major cause of illness and death in the United States. Annually, in the United States, 42,000 adult and 300 child deaths are attributed to vaccine-preventable diseases (United States Department of Health and Human Services, 2000). In 2015, 4,138 cases of *Haemophilus influenzae*, 1,390 cases of hepatitis A, 3,370 cases of acute hepatitis B, 188 cases of measles, 1,329 cases of mumps, 20,762 cases of pertussis, 5 cases of rubella, 29 cases of tetanus, and 9,789 cases of varicella were reported in the United States (Adams, 2017). However, the risk of contracting a VPD is not constant throughout the lifespan. For example, compared to adolescents and adults, young children are at increased risk for illness and death due to vaccine-preventable illness (Omer, Salmon, Orenstein, Dehart, & Halsey, 2009). For instance, age-specific incidence of pertussis cases in the U.S was 99.0 per 100,000 among infants less than 6 months of age and 37.2 per 100,000 among infants 6 to 11 months old in 2015. Age incidence of cases for adults 20 years and older was 1.9 per 100,000 (National Center for Immunization and Respiratory Diseases, 2017). Furthermore, young children 3 to 35 months old are greatest risk for severe rotavirus disease (National Center for Immunization and Respiratory Diseases, 2014). Overall, vaccination of young children helps to build immunity before infants and young children are exposed to potentially harmful or deadly VPDs (Centers for Disease Control and Prevention, 2013a).

Finally, vaccines are a critical component of preventive health care in children, and high rates of coverage are necessary for disease prevention (Diekema, 2012). Resurgences in VPD, such as pertussis, measles, mumps, and rubella, have occurred since the 1980s (Van Panhuis et al., 2013). Failure to vaccinate results in gaps in local vaccine coverage, and delays in vaccination can create pockets of the population with low rates of immunization. Herd immunity

is achieved when a certain proportion of a population is immune to an infectious agent. Vaccine refusal and delayed vaccination disrupts herd immunity, increasing risk of disease transmission and outbreaks (Malone & Hinman, 2003; Van Panhuis et al., 2013).

Rotavirus

The current rotavirus vaccines were first included in the schedule of routine childhood immunizations in 2006 (Cortese & Parashar, 2009). Although rotavirus-associated mortality was not considered high pre-vaccine, gastroenteritis among young children in the United States resulted in $1 billion in direct and indirect costs associated with 410,000 outpatient visits, more than 200,000 emergency department (ED) visits, and 55,000-70,000 hospitalizations annually (Charles et al., 2006; Cortese & Parashar, 2009; Malek et al., 2006; Parashar, Holman, Clarke, Bresee, & Glass, 1998; Tucker et al., 1998; Widdowson et al., 2007). Highest incidence of rotavirus infection was found among children aged three to 35 months, and the virus was responsible for 30-50% of gastroenteritis hospitalizations among children younger than five years (Centers for Disease Control and Prevention, 2015a).

Biologically, rotaviruses are double-stranded RNA viruses that cause infection in mammals; however, animal to human transmission resulting in clinical illness is unlikely. Rotavirus impacts both developed and developing countries similarly, though mortality associated with rotavirus infection is higher in developing countries. Predominant rotavirus strain differs by geographic location, and transmission occurs via the fecal-oral route through fomites or person-to-person transmission. The reservoir for the virus is the gastrointestinal tract and stool. The rotavirus also exhibits a temporal pattern, with increased incidence during the fall and winter seasons in temperate climates (Centers for Disease Control and Prevention, 2015a). The typical spatiotemporal pattern of seasonal infections involves epidemics that originate in heavily

populated areas before spreading to more rural locations (Pitzer et al., 2009). However, prior to vaccine introduction in the United States, rotavirus epidemic patterns were shown to originate in the Southwest during the months of November and December, progressing to the Northeast by April and May of each year (Centers for Disease Control and Prevention, 2015a). Environmental factors have been studied as potential drivers for epidemics of RV, but predictive models of post-vaccine RV found birth rate to be strongly associated with the timing of RV epidemics (Pitzer et al., 2009).

In general, rotavirus is a highly communicable disease and can remain viable for weeks to months without exposure to disinfectants. The virus enters the body through the mouth and typically has an incubation period of less than 48 hours. Communicability begins two days prior to the onset of symptoms and can last for up to 10 days after symptoms subside. Infections may be asymptomatic or may result in diarrhea of varied severity. Moreover, severe gastrointestinal upset can be associated with fever, vomiting, and dehydration that last between 3 to 7 days. Because of the non-specific features, laboratory testing is required to confirm rotavirus. Complications associated with rotavirus infection are generally more severe for infants and young children and may include severe diarrhea, dehydration, electrolyte imbalance, and metabolic acidosis. Immunocompromised children may suffer persistent rotavirus gastroenteritis (RVGE), which may compromise kidney, liver, and other organ system function (Centers for Disease Control and Prevention, 2015a).

The first rotavirus infection after age 3 months is typically the most severe; however, the initial infection will not result in lasting immunity to future infection in children. After the initial infection, only 38% of children are immune from future infection, though subsequent infections tend to be less severe. The first infection provides a high level of protection against RV diarrhea

and severe diarrhea in future infections. Though nearly 100% of children are infected with rotavirus by age 5, subsequent infections are not limited to early childhood and risks can remain through adulthood. Rotavirus infections are common within the same household, in hospitals, and within child care settings, making it difficult to contain once infection occurs (Centers for Disease Control and Prevention, 2015a).

Rotavirus vaccines. Vaccination of very young children is designed to mimic the first natural rotavirus infection, thus providing protection against severe disease, as well as associated complications and healthcare utilization during subsequent RV infection (Cortese & Parashar, 2009). In 1998, the ACIP recommended the first rotavirus vaccine, Rotashield® (RRV-TV). However, based on post-licensure studies, the vaccine was quickly withdrawn from the market due to a substantial increase in the age-dependent risk of intussusception, a serious condition in which a portion of the intestine slides into another often resulting in infection and death of infected tissue (Centers for Disease Control and Prevention, 1999a, 1999b; Murphy et al., 2001). Currently, there are two licensed rotavirus vaccines for childhood vaccination available in the United States (Centers for Disease Control and Prevention, 2017b; Cortese & Parashar, 2009).

The first vaccine, RotaTeq® (RV5), was licensed in 2006. RV5 is a live, oral vaccine that is comprised of five reassortant rotaviruses that were developed from both human and bovine parent strains (Cortese & Parashar, 2009). RotaTeq® is highly efficacious against RVGE and severe RGVE. In a sub study of the Rotavirus Efficacy and Safety Trial (REST) among Finnish and American infants, RV5 efficacy was 98-100% against severe RVGE through the first rotavirus season after vaccination and 88% through the second season. Efficacy against RVGE of any severity was 74.0% through the first RV season. Further analysis of REST data found that the three-dose series of RV5 has significantly reduced RVGE-associated health care utilization.

Efficacy of the vaccine against RVGE hospitalizations was 95.8% and 93.7% against RVGE emergency department visits. Outpatient clinic visits for RVGE decreased by 86%. Furthermore, the vaccine was also almost 60% efficacious against any-cause gastroenteritis hospitalization after only one dose, and clinical trials found no increase in risk of intussusception after RV administration when compared to placebo (Block et al., 2007; Vesikari, Matson, et al., 2006).

The second vaccine, Rotarix® (RV1), a monovalent human rotavirus vaccine, is a live, oral vaccine that was licensed in 2008 and added to the ACIP recommendation for the prevention of RVGE in infants and children in 2009 (Cortese & Parashar, 2009). In clinical trials in Finland and Latin America, two doses of RV1 were found to be highly efficacious (84.7%) against severe rotavirus gastroenteritis in infants until one year of age, and efficacy until age 2 was 80.5% (Ruiz-Palacios et al., 2006). European clinical trials found efficacy of the RV1 series against RVGE of any severity through the first RV season to be 87.1% and 95.8% against severe RVGE. Efficacy through the second year was 78.9% against RVGE of any severity and 90.4% against severe RVGE. RV1 efficacy against hospitalization for all-cause gastroenteritis was 74.7%, and the vaccine series was not found to increase risk of intussusception in infants (Vesikari et al., 2007).

In 2006, an analysis of the projected impact of a national RV vaccine program estimated that the RV5 vaccination, given in a three-dose series to a birth cohort followed until age five, would result in the reduction of 13 deaths, 255,000 physician visits, 137,000 ED visits, and 44,000 hospitalizations. Although routine RV5 vaccination would not be a cost-saving intervention, it was still considered cost-effective after accounting for costs of vaccine administration (Widdowson et al., 2007). Further analysis indicated that the two-dose series of RV1 was similar in cost-effectiveness as RV5 (Cortese & Parashar, 2009). Results of the cost-

effectiveness analysis, combined with the high level of RV morbidity, as well as the fact that initial infection is protective against severe illness during subsequent RV infection, prompted the ACIP to recommend RV vaccination as part of the routine childhood immunization program in the United States (Cortese & Parashar, 2009).

The ACIP recommends routine vaccination with RV vaccine, without preference for RV5 or RV1. Both vaccines are to be administered orally, RV5 in a three-dose series at 2, 4, and 6 months of age or RV1 as a two-dose series at 2 and 4 months of age. Dose 1 should not be administered prior to 6 weeks of age or after and infant has aged 14 weeks 6 days. The minimum interval between doses is four weeks, and all doses must be administered by 8 months 0 days. Infants 15 weeks 0 days and older should not initiate either RV vaccine series. Simultaneous administration of RV, DTaP, PCV, Hib, IPV, and hep B vaccines is acceptable. Use of the same product for the duration of the series is preferred. However, in instances where product is not known or any RV dose was RV5, three doses in total should be administered prior to the maximum age restriction of 8 months 0 days of age (Centers for Disease Control and Prevention, 2017b; Cortese & Parashar, 2009). Notably, research has indicated that a greater proportion of infants complete the two-dose RV1 series when compared to the three-dose RV5 series (Calnan et al., 2016; Krishnarajah, Davis, Fan, Standaert, & Buikema, 2012; Krishnarajah, Landsman-Blumberg, & Eynullayeva, 2015).

Impact of rotavirus vaccination. Data from the Center for Disease Control and Prevention's National Respiratory and Enteric Virus Surveillance System (NREVSS) indicate a nationwide 57.8%-89.9% decrease in rotavirus detection between 2007-2014. (Aliabadi et al., 2015). After implementation of the RV vaccine, the onset and peak of seasonal RV activity has been delayed, and annual epidemics have been replaced with biennial peaks of increased RV

activity and seasonality similar to pre-vaccine patterns (Pitzer et al., 2009; Tate et al., 2009). When the threshold of a RV season was achieved, it started later, had a lower peak, and was shorter than RV seasons prior to vaccine introduction (Aliabadi et al., 2015).

Studies on vaccine effectiveness indicate that both a partial and complete RV vaccine series provide highly effective and lasting protection against severe rotavirus disease. In study results using active surveillance as part of the CDC-funded New Vaccine Surveillance Network (NVSN), vaccine effectiveness for the complete 3-dose series of RV5 in children under three years of age was 92% effective against RVGE hospitalizations and ED visits during the first two RV seasons after vaccine implementation (Donauer et al., 2013). In further analysis of data from the NVSN, researchers found that among children under 8 years of age receiving any dose of RV1 or RV5 was 78% effective against severe RVGE that required hospitalization or a visit to the ED. Vaccine effectiveness for one dose of RV5 was 68%, 78% for two doses, and 80% for the complete 3-dose series. Similarly, effectiveness for the two-dose RV1 series was 80%. Significant effectiveness was noted with RV5 for seven years and three years in RV1. Notably, analysis of long term consistency in RV1 effectiveness was limited by the data available, as the vaccine had only been in use for three years when the study began (Payne et al., 2015). Vaccine effectiveness for the complete series of RV1 or RV5 did not vary significantly from 2010-2013 (Payne et al., 2013; Payne et al., 2015). Similarly, A case-control study of RV5 effectiveness in children under 2 years in a large urban area in the United States found the complete three-dose series to be 85-89% effective against severe RVGE. Partial immunization of one or two doses was 69% effective against RVGE hospitalization and 81% effective against RVGE-associated ED visits (Boom et al., 2010). Active surveillance in three U.S counties found RV5 to be highly effective (> 85%) after both two and three doses against acute rotavirus gastroenteritis that

required hospitalization or visits to the emergency department among children in the three RV seasons after RV5 implementation (Staat et al., 2011). Desai et al. (2010) found high levels of vaccine effectiveness in the prevention of hospitalizations due to RVGE among both partially (93-94%) and completely (96-99%) vaccinated children under age 3 (Desai, Esposito, Shapiro, Dennehy, & Vázquez, 2010). Moreover, analysis from the Rotavirus Efficacy and Safety Trial (REST) found that RV5 provided protection against RVGE hospitalization and emergency department visits 14 days after the first dose (Dennehy et al., 2011). In a follow-up study to REST, researchers found vaccine efficacy against of 93.9% against RVGE hospitalization and emergency department visits among infants aged 4 to 11 months, vaccine efficacy of 94.4% in children aged 12 to 23 months, and vaccine efficacy of 85.9% in children aged 24 to 35 months (Vesikari, Karvonen, Ferrante, & Ciarlet, 2010). Research of the effectiveness of less than a full series of RV vaccine is identified as an area in need of study by the ACIP (Cortese & Parashar, 2009).

Prior to vaccine implementation, rotavirus was the primary cause for a significant proportion virus related hospitalization, treatment in emergency departments, or treatment in outpatient clinics for acute gastroenteritis among children under 5 years of age (Mast et al., 2010). In follow up to the Rotavirus Efficacy and Safety Trial (REST) in Finland, researchers found that RVGE hospitalizations and emergency department visits were decreased by almost 94% for up to three years after receipt of the last RV vaccine dose. A 62.4% decrease in all-cause AGE hospitalizations and emergency department visits was also noted (Vesikari et al., 2010). As early as two years after the licensure of RV5 in the United States, there was an estimated decline of 40,000-60,000 hospitalizations, the equivalent of a 46% decrease in diarrhea-coded hospitalizations. An examination of acute gastroenteritis (AGE) hospitalizations from eighteen

states among children under age 5 found that the highest rate of acute gastroenteritis was among children aged 6 to 11 months in each of the years (2000-2006) prior to RV5 introduction. Sizable decreases in AGE hospitalization rates were noted in the two seasons following introduction of RV5. Median rates of AGE hospitalizations were 16% and 45% lower in 2007 and 2008, respectively. The largest decreases in AGE hospitalizations were among children ages 3 to 11 months (Curns et al., 2010). Significant decreases in all-cause and rotavirus-coded gastroenteritis hospitalizations were also noted in analysis of the State Inpatient Database (SID), a part of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project. Annual average of all-cause gastroenteritis hospitalizations pre-vaccine (74.0 per 10,000) decreased 31% in 2008 and 51% in 2009. Rotavirus-coded gastroenteritis hospitalizations (15 per 10,000) decreased 71% in 2008 and 62% in 2009. The largest decreases were found among infants ages 6 to 11 months, the age group that accounted for the largest rates of RV pre-vaccine (Desai et al., 2012).

Indirect benefits of rotavirus vaccination have also been shown in the peer-reviewed literature. Though RV vaccine effectiveness increases with number of doses, reduced risk of disease in partially vaccinated and unvaccinated children has been noted (Buttery et al., 2011; Curns et al., 2010; Panozzo et al., 2009; Payne et al., 2011). A comparison of acute gastroenteritis (AGE) hospitalizations among children under age 5 found the largest decreases in AGE hospitalizations were among children ages 3 to 11 months, though decreases were noted in all age groups. The study was conducted using data from the two years after RV5 implementation, and these decreases may imply indirect benefits to children too old for RV vaccination (Curns et al., 2010). A separate analysis of RVGE hospitalizations among children less than 36 months old found that, compared to rates in 2006, there was a statistically significant

reduction of 87-96% in RV-associated hospitalizations among all age groups in 2008, which included children too old to receive the RV vaccination (Payne et al., 2011). Further analysis also revealed indirect protection against moderate to severe rotavirus disease in older siblings and young parents of RV vaccinated infants, likely caused by the disruption of transmission among households and within communities (Cortese, Dahl, Curns, & Parashar, 2014; Payne et al., 2011).

Recent research on the outcomes of RV vaccination among Medicaid-insured children aged 8 to 60 months found significant differences in incidence of RV, and RV-associated healthcare utilization, as well as costs between different levels of vaccine series completion (Krishnarajah, Duh, Korves, & Demissie, 2016). Researchers also found that RV infection was two times higher in unvaccinated children when compared to children with complete vaccination against RV per ACIP recommendations. Members of the completely vaccinated cohort had received two RV1, three RV5, or three mixed type RV vaccine doses between 6 weeks and 8 months of age. Rotavirus incidence (per 10,000 person-years) was 7.5, 9.0, and 14.6 in the completely vaccinated, incompletely vaccinated, and unvaccinated cohorts, respectively. The incidence rate ratio of first RV episode for completely vaccinated to unvaccinated children was 0.52 (0.32-0.83) and for incompletely vaccinated to unvaccinated children, the incidence ratio was 0.61 (0.44-0.87). Incidence of RV-coded emergency department visits, and outpatient visits among completely and incompletely vaccinated children were significantly lower when compared to the unvaccinated cohort. Furthermore, there was a significantly lower incidence in RV-coded hospitalizations between the incompletely vaccinated and unvaccinated cohorts. Conversely, incidence of diarrhea-coded hospitalizations, emergency department, and outpatient visits were significantly higher in the completely and incompletely vaccinated cohorts compared

to the unvaccinated cohort of children. When compared to unvaccinated children, mean cost differences were statistically significant between both completely vaccinated and incompletely vaccinated children. Additionally, when compared to a cohort of children unvaccinated against RV, mean costs for the first rotavirus episode was $4.26 lower for completely vaccinated cohort members and $3.77 lower per cohort member among incompletely vaccinated children. Mean cost for the first diarrhea episode among Medicaid insured children was $21.69 lower among completely vaccinated children when compared to the unvaccinated cohort (Krishnarajah et al., 2016).

An estimated $187 million reduction in costs associated with laboratory-confirmed RV emergency department visits and hospitalizations each year in the United States is attributed to RV vaccine implementation. Pre-vaccine, laboratory confirmed RV-associated hospitalizations cost $91 million and emergency department visits cost and $192 million annually. Estimated annual cost for RV-associated hospitalizations decreased to $31 million, and RV-associated emergency department visits decreased to $65 million post-vaccine (Kilgore et al., 2013). In a study of commercially insured children from 2007-2009, RV5 vaccination was estimated to have saved $278 million in treatment costs via a reduction of approximately 64,855 diarrhea-associated hospitalizations among children under 5 years of age (Cortes et al., 2011). Future studies and surveillance are necessary to further examine both direct and indirect effects of RV vaccination on health care utilization and costs.

Issues in Measurement

Although, rotavirus is not a reportable disease in the United States (Centers for Disease Control and Prevention, 2015a), national RV surveillance is conducted through the National Respiratory and Enteric Virus Surveillance System (NREVSS), the New Vaccine Surveillance

Network (NVSN), the National Rotavirus Strain Surveillance System (NRSSS), and national health utilization datasets. It is important to monitor vaccine impact on RV disease morbidity and mortality for use in the evaluation of vaccine effectiveness, the identification of under-vaccinated pockets of children, and to monitor RV vaccine safety (National Center for Immunization and Respiratory Diseases, 2014). To monitor RV disease and impact of the RV vaccine program in local areas, the ACIP recommends surveillance at sentinel hospitals or by discharge databases (Cortese & Parashar, 2009). Outcomes of RV vaccination are also evaluated via immunization information systems and health claims databases; however, it is important to note that each is not without its limitations. Analysis of the accuracy of regional immunization information system data and its use in the evaluation of RV5 effectiveness found that data in the immunization information system was generally less complete than records from vaccination providers, which could lead to underestimation of RV doses administered and resulting vaccine effectiveness (Sahni et al., 2010). A study of the accuracy of administrative claims data to identify RV vaccine information found a positive predictive value of 87.1%. Alternatively, 12.9% of first RV5 doses identified through claims data were inaccurate in dose number or date of administration (Quinlan, Lanes, Holick, & Mast, 2015).

When compared to surveillance data, the RV-specific diagnosis code in hospital discharge and claims databases greatly underestimates the incidence and impact of RV. Prior to the introduction of the RV-specific diagnosis code, indirect methods were used to estimate RV-associated health care utilization (Hsu et al., 2005). The RV-specific ICD code allows for direct estimation; however, use of the RV-specific diagnosis code underestimates RV-associated health care utilization (Hsu et al., 2005). Pre-vaccine, researchers found that only 11% of laboratory-confirmed cases of RV in children, which were identified through active surveillance, were

coded with the RV-specific ICD-9 code of 008.61. This percentage was lowest among acute gastroenteritis cases presenting to the emergency department or outpatient clinics. Sixty-one percent of children assigned an acute gastroenteritis code during hospitalization, visits to the emergency department, or in an outpatient clinic tested positive for RV (Mast et al., 2010). Hsu et al. (2005) found the ICD-9 RV-specific diagnosis code of 008.61 to be 97% specific and only 47% sensitive among hospitalized children less than 5 years of age (Hsu et al., 2005).

Simultaneous Administration of Childhood Vaccines

Simultaneous administration of all age-appropriate vaccines is crucial for the achievement of coverage targets and to ensure children remain up-to-date during periods of increased susceptibility to vaccine preventable disease. The elimination of missed opportunities for vaccination could significantly improve vaccine coverage levels, resulting in decreased risk of VPD among children (Zhao, Smith, & Hill, 2016). Upper age limits for the RV vaccine may result in lower coverage and could impact other routine childhood vaccinations due at same age intervals.

Coverage of RV vaccination by dose and its impact on the receipt of DTaP and PCV vaccines were evaluated in an Australian study of infants under 12 months of age. Researchers found that timeliness of both DTaP and PCV doses improved after the introduction of the RV vaccine; however, final dose coverage of RV vaccine was 7% lower than that of three doses of DTaP. More than 95% of vaccinated children received a timely first RV vaccine dose, and the proportion of infants who received a final dose of RV1 was higher than for the final dose of RV5, which seems to indicate that the upper age limit restriction for RV vaccine doses may limit RV vaccine coverage compared to other routine childhood vaccines (Hull et al., 2013). Analysis of claims data in the United States found a high correlation (r=0.76) between number of DTaP

and RV received by commercially-insured children (Panozzo et al., 2013). When compared to DTaP and PCV vaccinations, recent evaluation of RV vaccine uptake over time among infants aged 5 months found coverage of the RV vaccine was six percentage points lower than DTaP and four percentage points lower than PCV. Fifteen percent of infants who had received another non-influenza routine vaccination did not receive the RV vaccination. Among those, 45% had received another routine immunization between the ages of 6 weeks and 14 weeks, which is the period of eligibility for the first dose of the RV series. Approximately one third of the difference between coverage in DTaP and RV by age five months could be the result of the maximum age restriction of 14 weeks 6 days for the first RV dose. This age restriction highlights the importance of monitoring coverage among young infants, as differences in young infancy in multi-dose vaccinations become further amplified when measured at age 2 years (Pringle, Cardemil, Pabst, Parashar, & Cortese, 2016).

Predictors of Rotavirus Vaccination

Consequently, completion of DTaP vaccine series is a significant predictor of RV vaccination compliance. In addition, as coverage of one vaccine is increased, there is an associated increase in the coverage and in the compliance to dosing schedules of other childhood vaccines (Calnan et al., 2016; Hull et al., 2013; Krishnarajah et al., 2015; Panozzo et al., 2013; Wendy, 2012). Sociodemographic factors previously associated with childhood vaccination include first born child, race, number of children in the family, poverty level of the family, urbanicity, change of residence since birth, geography (region), mother's marital status, maternal education level, maternal age, type of insurance (private, public, or uninsured), number of vaccination providers, and type of vaccination provider (pediatrician or family physician) (Zhao et al., 2016). Rotavirus vaccination-specific predictors in the peer-reviewed literature include

receipt of the DTaP vaccine, completion of the DTaP series, birth year, RV vaccine type, pediatrician as vaccination provider (rather than family physician), number of children under 10 years of age in the same household, and living in a large metro area as compared to small urban or rural residence (Calnan et al., 2016; Krishnarajah et al., 2015; Panozzo et al., 2013).

Disparities in Rotavirus Vaccine Coverage and Illness

Though rotavirus-related morbidity has been reduced since vaccine introduction, disparities in rotavirus vaccine coverage and rotavirus-related morbidity persist in the United States (Hill et al., 2015). Risk factors for RV gastroenteritis hospitalization in the U.S. include low birth weight, children 24-59 months of age in childcare, uninsured children less than 24 months of age, Medicaid-insured children less than 24 months of age, another child in the home less than 24 months of age, maternal age of less than 25 years, and maternal education level of less than a high school education. (Dennehy et al., 2006). Disparity by region, rural residence, race/ethnicity, income, and type of insurance have been widely demonstrated.

Geographic disparities. Variability in vaccine coverage between regions and states of the United States is well documented. Children born in the Southern United States are 1.27 times more likely to be immunized than children born in the West (Crouch & Dickes, 2015). Rotavirus vaccine coverage estimates among children aged 19 to 35 months for the state of Alabama ranged from 63.4-85.4% from 2010-2015, while national coverage estimates ranged from 59.2-73.2% during the same time-period (Centers for Disease Control and Prevention, 2011a, 2012b, 2013b, 2014, 2015b, 2016b). The most recent data from 2015 estimates RV vaccine coverage in Alabama at 76.2%, which is three percentage points higher than national RV coverage among children aged 19 to 35 months (Centers for Disease Control and Prevention, 2016b). Though coverage estimates for the state are higher than national estimates, RV vaccine coverage in

Alabama has not reached the *Healthy People 2020* goal of 80%. Furthermore, analysis of 2007-2014 data from the National Respiratory and Enteric Virus Surveillance System (NREVSS) found that, in contrast to other areas, onset and duration of the RV in the Southern region of the United States continued to vary and was often comparable to pre-vaccine years (Aliabadi et al., 2015). Consistent seasonality in the Southern United States may indicate that coverage must continue to increase to impact RV morbidity in the South.

In addition, it is imperative that local level coverage data is evaluated to identify areas of unvaccinated and under-vaccinated children (Hill, 2016). The impact of RV vaccination on transmission within families and communities will likely vary as susceptible children accumulate (Payne et al., 2011). Results from the 2015 NIS found that children in more rural areas had lower estimates of RV vaccine coverage (Hill, 2016). In 2015, national RV coverage estimates for children aged 19-35 months for Metropolitan Statistical Area (MSA) Noncentral Cities (75.1%) were 6.5 and 2.4 percentage points higher than that for Non-MSA (68.6%) and MSA Central Cities (72.7%), respectively. In Alabama, 2015 estimates for Non-MSA areas were 64.3%, which is 14.5 and 15.8 percentage points lower than RV vaccine coverage for MSA Central Cities and MSA Noncentral Cities in the state, respectively (Centers for Disease Control and Prevention, 2016b). Analysis of RV vaccine uptake found children living in small urban or rural areas are less likely to receive RV vaccination when compared to children in large metro areas (Panozzo et al., 2013).

Racial/Ethnic group disparities. Among vaccines recommended for routine administration in early childhood beginning in 1995, disparities in coverage between non-Hispanic white and children of other racial/ethnic groups have been reduced or eliminated (Walker, Smith, & Kolasa, 2014). Data from the 2014 and 2015 NIS revealed lower estimated

RV vaccine coverage for non-Hispanic black children compared to non-Hispanic white children (Hill, 2016; Hill et al., 2015). In 2015, national rotavirus vaccine coverage estimates for non-Hispanic white children aged 19 to 35 months were 74.6% when compared to 69.7% among non-Hispanic black children, although this difference was not statistically significant after controlling for poverty status (Centers for Disease Control and Prevention, 2016b; Hill, 2016). However, the difference between the two racial groups remained statistically significant after an adjustment for poverty status in 2014 (Hill et al., 2015). Alabama RV coverage estimates for non-Hispanic white children were 78.5% in 2015, which was 6.1 percentage points higher than the estimate for non-Hispanic black children (72.4%) in the state (Centers for Disease Control and Prevention, 2016b). Researchers who evaluated completion and compliance of RV vaccination among Medicaid-enrolled infants found significant differences in the proportion of infants vaccinated against RV by race. The largest proportion unvaccinated against RV was Hispanic infants (52-54%), followed by black infants (42-45%), and then white infants (36-39%) (Krishnarajah et al., 2015).

Socioeconomic disparities. Disparities in RV vaccine effectiveness and coverage have been noted among children from low income countries, as well as low-income households. Clinical trial data have shown differences in vaccine efficacy in high, middle, and low-income countries. Vaccine efficacy that exceeds 90% in high income countries decreases to 72-83% in middle income countries. Among low income countries in Africa and Asia, efficacy is as low as 39 to 49% (Armah et al., 2010; Linhares et al., 2008; Lopman, Pitzer, et al., 2012; Madhi et al., 2010; Vesikari, Giaquinto, & Huppertz, 2006; Vesikari, Karvonen, et al., 2006; Zaman et al., 2010). Post-licensure studies found the RV vaccine to be highly effective (>85%) in high income countries, a result that was like RV vaccine clinical trials. Effectiveness of the vaccine was

sustained through two years of life (Staat et al., 2011). Mathematical models used to explain reduced efficacy in low income countries found a decline in efficacy at 3 years of age and insignificant efficacy by age 4. Results indicate that lower socioeconomic countries have lower vaccine effectiveness and a shorter duration of protection from RV vaccination, and vaccination does not provide protection against symptomatic disease in subsequent infection as readily in low income countries.(Lopman, Payne, et al., 2012).

The NIS has revealed disparities in vaccination coverage among young children living below the poverty level since 2009. Lower coverage among families living below the poverty level for vaccine series that require 3-4 doses has been noted. The income disparity in RV vaccine coverage is among the largest of the routine childhood vaccinations. Children living below the poverty level had RV vaccine coverage 14.1 and 10.0 percentage points lower than children at or above the poverty level in 2014 and 2015, respectively (Hill, 2016; Hill et al., 2015). Rotavirus vaccine coverage of children living below the poverty level in Alabama (72.0%) was 5.5 percentage points lower than children living at or above the poverty level (77.5%) in 2015 (Centers for Disease Control and Prevention, 2016b). While racial disparities in vaccine coverage were decreased after an adjustment for MSA status, all coverage disparities by level of income remained significant (Hill, 2016).

Disparities by insurance type. In 2016, 38% of children in the United States younger than 19 years of age were enrolled in Medicaid. Among children 0-18 years of age in Alabama, 55.3% were Medicaid eligible in 2016 (Alabama Medicaid Agency, 2017; Henry J Kaiser Family Foundation, 2017). Prior to vaccine introduction, hospital surveillance from three large children's hospitals found that uninsured and Medicaid-insured children under age 5 were two times as likely to be hospitalized for RVGE (Dennehy et al., 2006). Analysis of the Kids'

Inpatient Database from 2000-2003 found that Medicaid enrolled children under age 5 years had greater rates of RVGE-associated hospitalizations, as well as greater lengths of and charges per stay than non-Medicaid enrolled children. Disproportionate disease burden highlights the importance of RV vaccination among Medicaid-enrolled children (Ma, El Khoury, & Itzler, 2009). In an analysis of Medicaid claims data for children 6 to 8 months old from four U.S. states in 2008-2012 (*n*=695,612), researchers found that 40% of infants did not receive a RV vaccine and only 46% of infants who received a RV vaccine dose were compliant with the ACIP recommended dosing schedule. Similar analysis of a large multi-state Medicaid database from 2008-2013 (*n*=658,219) found that 40.4% of infants did not receive a RV vaccination. Of the infants who received RV vaccine doses, 28.2 % were compliant with ACIP guidelines (Calnan et al., 2016).

Since vaccine introduction, RV incidence and RV-associated health care utilization decreased among both commercially and Medicaid-insured children (Krishnarajah, Demissie, Lefebvre, Gaur, & Sheng Duh, 2014). However, RV disease burden, incidence of RV-coded hospitalizations, emergency department visits, and outpatient visits are higher among Medicaid-insured children (Krishnarajah et al., 2014). Analysis of commercial and Medicaid claims among children under 5 years of age found that only 66.2% of commercially-insured children and 32% of Medicaid-insured children had received at least one dose of RV vaccine by 8 months of age. Among commercially-insured children, 44% completed the RV vaccine series per ACIP recommendations, compared to only 12.9% of Medicaid-insured children. Researchers also found lower disease reduction among Medicaid-insured children (Krishnarajah et al., 2016). Incidence of RV infection among completely vaccinated and incompletely vaccinated commercially-insured children was 3.3 and 4.0 (per 10,000 person-years), respectively. Among

Medicaid-insured children, lower disease reduction was evidenced by larger incidence of RV infection, with an incidence of 7.5 (per 10,000 person-year) in completely vaccinated children and 9.0 (per 10,000 person-year) in incompletely vaccinated children (Krishnarajah et al., 2016).

Research Purpose

In summary, results from the National Immunization Survey provide important insight into vaccination coverage at the national and state level. Examination of local-level coverage data can identify areas of increased susceptibility to disease due to low RV vaccine coverage. Coverage estimates from the NIS indicate consistently lower RV vaccine coverage among more rural and more impoverished children (Hill, 2016). In 2016, approximately 24% of Alabama's population lived in rural areas, and over half of Alabama children were Medicaid eligible (Alabama Medicaid Agency, 2017; United States Department of Agriculture Economic Research Service, 2017). Studies indicate fewer rotavirus vaccinations and a disproportionate rotavirus disease burden in Medicaid-insured children (Krishnarajah et al., 2014; Krishnarajah et al., 2016; Ma et al., 2009). Estimates produced by the NIS highlight disparities in Alabama rotavirus vaccination coverage by racial/ethnic group, rural residence, socioeconomic status, and type of insurance coverage. Efforts to further characterize these disparities and improve rotavirus vaccination coverage in the state is necessary for further decreases in rotavirus disease burden and associated health care costs.

As can be gleaned from this review, vaccine preventable diseases remain important threat to public health and efforts are needed to fill in the gaps in the literature. Therefore, the objectives of the present study are to 1) Examine the association between rurality and the initiation and completion of the ACIP-recommended rotavirus vaccine series among Medicaid-insured children 2) Examine potential predictors of initiation and completion of the ACIP-

recommended rotavirus vaccine series among Medicaid-insured children and 3) Examine differences in rotavirus-associated health care utilization and cost between Medicaid-insured children who are partially vaccinated and those who are completely vaccinated against rotavirus according to ACIP-recommendations.

ARTICLE 1: RURALITY AND RECEIPT OF THE ROTAVIRUS VACCINE SERIES IN A MEDICAID POPULATION

Introduction

Rotavirus (RV) is the leading cause of severe diarrhea worldwide among children younger than five years (Centers for Disease Control and Prevention, 2015a; World Health Organization, 2013). Prior to the introduction of routine vaccination, rotaviruses were the leading cause of severe gastroenteritis among young children in the United States, and Rotavirus Gastroenteritis (RVGE) was a primary reason for hospitalizations and visits to the emergency department (Centers for Disease Control and Prevention, 2015a; Dennehy, 2005). The direct and indirect costs of RV disease were estimated at $1 billion, which was attributed to an estimated three million cases of rotavirus disease occurring each year pre-vaccine. These infections were responsible for up to 70,000 hospitalizations, more than 200,000 visits to the emergency department, and more than 400,000 outpatient physician visits annually in the United States (Centers for Disease Control and Prevention, 2015a; Cortese & Parashar, 2009; Fischer et al., 2007; Glass et al., 1996; Widdowson et al., 2007; World Health Organization, 2013).

The Advisory Committee on Immunization Practices (ACIP), medical and public health experts who provide annual vaccine recommendations to the Centers for Disease Control and Prevention (CDC), recommended routine RV vaccination of infants in 2006, following the licensure of RotaTeq® (RV5) (Merck & Co., Inc.) (Centers for Disease Control and Prevention, 2012a; Parashar, Alexander, Glass, & Practices, 2006). Following the licensure of Rotarix® (RV1) (GlaxoSmithKline Biologicals) in 2009, the ACIP revised the former recommendations

(Cortese & Parashar, 2009). Current recommendations include three doses of RV5 administered at 2, 4, and 6 months of age or two doses of RV1 administered at ages 2 and 4 months. The first dose should not be administered prior to 6 weeks 0 days or after 14 weeks 6 days of age. No dose in the RV vaccine series should be administered after 8 months 0 days of age due to increased risk of intussusception noted in studies of a RV vaccine that is no longer licensed for use (Cortese & Parashar, 2009).

Simultaneous administration of the RV vaccine with other routine childhood vaccinations is recommended. Despite this recommendation, RV vaccine coverage is considerably lower when compared to other vaccines recommended for administration during the same age ranges (Cortese & Parashar, 2009; Hull et al., 2013; Tate, Cortese, Payne, Curns, Yen, Esposito, Cortes, Lopman, Patel, & Gentsch, 2011). The *Healthy People 2020* coverage target for the complete ACIP-recommended RV vaccine series among children aged 19-35 months is 80% (United States Department of Health and Human Services, 2000). Data obtained during the National Immunization Survey (NIS) used to estimate coverage for the complete RV vaccine series among children aged 19-35 months produced estimates considerably lower than the 80% target that ranged from 59.2% in 2010 to 74.1% in 2016 (Centers for Disease Control and Prevention, 2011a, 2012b, 2013b, 2014, 2015b; Hill, 2016; Hill et al., 2017).

Additionally, rural residents have less access to care than suburban or urban residents and reduced access to care has been associated with decreased preventive health care, as well as poor health outcomes (Ferdinand, Johnson, Brown Speights, & et al., 2015). Rural children are less likely to have had a preventive health care visit during the past year, and geographic disparities in vaccine coverage can increase disease susceptibility (Hill et al., 2015; United States Department of Health and Human Services, 2015). Furthermore, analyses of coverage for ACIP-

recommended vaccinations for young children indicate disparities among rural residents. Specifically, NIS-produced RV vaccine coverage estimates are consistently lower for children who reside in more rural locations (Centers for Disease Control and Prevention, 2011a, 2012b, 2013b, 2014, 2015b; Hill, 2016). An analysis of privately (commercially) insured children found that children who lived in small urban or rural areas were significantly less likely to receive RV vaccination when compared to children who resided in large metro areas (Panozzo et al., 2013). Similarly, a study of hepatitis A vaccination among young children in Michigan found rural children less likely to receive vaccination when compared to children in non-rural areas (Weston & Enger, 2010).

Moreover, studies indicate that low-income and Medicaid-insured children have RV vaccine coverage that is lower than their commercially-insured counterparts (Calnan et al., 2016; Krishnarajah et al., 2012; Krishnarajah et al., 2016; Krishnarajah et al., 2015). In 2016, the NIS found Medicaid-insured children had a coverage rate 12 percentage points lower than their privately-insured counterparts (Hill et al., 2017). Consequently, children enrolled in Medicaid face a disproportionate RV disease burden (Ma et al., 2009). The incidence of RV-associated hospitalizations, emergency department visits, and outpatient physician visits and resulting costs are higher among Medicaid-insured children (Dennehy et al., 2006; Krishnarajah et al., 2014; Krishnarajah et al., 2016; Ma et al., 2009).

As rural and low-income children are less likely to complete the RV vaccine series per ACIP recommendations, the examination of a partial RV vaccine series is increasingly important in the prevention of RV disease outbreaks and the maintenance of herd immunity. The full RV vaccine series is highly effective, with effectiveness against severe rotavirus disease improving with each dose in the series (Boom et al., 2010; Donauer et al., 2013; Payne et al., 2013; Payne et

al., 2015; Staat et al., 2011). Recent studies examined differences between RV-associated health care utilization between unvaccinated cohorts and completely vaccinated or incompletely vaccinated cohorts; however, these studies did not make comparisons between children completely vaccinated according to ACIP recommendations and incompletely vaccinated children (Krishnarajah et al., 2016; Krishnarajah, Kageleiry, Korves, Lefebvre, & Duh, 2017). The ACIP has recommended additional research on the effectiveness of a partial RV vaccine series, which coupled with lagging coverage rates, makes study of incompletely vaccinated children timely (Cortese & Parashar, 2009). Therefore, the purpose of the present study is to assess initiation and completion of the RV vaccine series per ACIP recommendations by rurality of residence among Medicaid-insured children.

Methods

Data source. The present study used a retrospective cohort study design which utilized a Medicaid database that includes longitudinal claims history, health care provider information, and enrollee eligibility by month for enrollees in the state of Alabama. A monthly average of 580,751 children, 45.0% of children in the state, were eligible to enroll in the Alabama Medicaid program during 2016 (Alabama Medicaid Agency, 2017). Analysis was limited to children enrolled in the program between January 1, 2010 through November 30, 2017.

Study population. Infants born between January 1, 2010 and April 1, 2017 and continuously enrolled in the state Medicaid program from birth until at least eight months of age were included in the study population. Continuous enrollment was defined as enrollment every month from birth to age 8 months 0 days and was necessary to capture all encounters for rotavirus vaccination among enrolled infants. A 30-day gap in eligibility immediately following birth was deemed acceptable. Due to lack of time for follow-up, infants born after April 1, 2017

were excluded from the study population. Infants who received any dose of RV vaccine prior to the ACIP-recommended minimum age for first RV vaccine dose of age 6 weeks 0 days were excluded from the analysis.

Measure of rurality. Rurality of residence was defined using Rural Urban Commuting Area (RUCA) codes, a classification of census tracts that uses commuting distances and population density to describe sub-county geographic areas. Zip code approximations were utilized to link enrollee residence in the Medicaid database to the appropriate RUCA code (United States Department of Agriculture, 2016). RUCA codes were condensed into four categories using categorization A: Urban focused, large rural city/town focused (micropolitan), small rural town focused, and isolated small rural town focused (Rural Health Research Center, 2007)

Measure of rotavirus series initiation and completion. The receipt of a RV vaccine was identified in the claims data using the Current Procedural Terminology (CPT) codes for RV5 (90680) and RV1 (90681) (American Academy of Pediatrics, 2016). As defined by current ACIP recommendations, completion of the RV vaccine series was defined as receipt of three doses of RV5, two doses of RV1, or three mixed type doses (combination of RV5 and RV1) by age 8 months 0 days. Initiation of the RV vaccine series was defined as the receipt of ≥1 dose of either RV5 or RV1 prior to 14 weeks 6 days of age, the maximum age for the first dose of RV vaccine per current ACIP recommendations.

Statistical analysis. Demographic characteristics were summarized for the entire population and by RV vaccination status and included frequencies and proportions for categorical variables. A modified Poisson regression using a log link function was applied to evaluate relative risks between levels of rurality of residence and the binary outcome variables,

RV series initiation and RV series completion. The modified Poisson utilized a robust error variance to estimate standard errors for relative risk, which are overestimated when Poisson regression is used with binary outcome measures (Greenland, 2004; Spiegelman & Hertzmark, 2005; Zou, 2004). Using urban residence as the reference group, risk ratios and 95% confidence intervals (CI) for rurality of residence are presented. Data analysis for the present study was completed using SAS® software version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Population characteristics. Characteristics of the study population are summarized in Table 3. A total of 293,458 infants met inclusion criteria and were included in the study population. Only 56.30% (*N*=165,225) of infants completed the RV vaccine series by the 8 months 0 days of age. Over 83% of the study population was comprised of black or white infants. Almost 77% (*N*=225,541) of infants initiated the RV vaccine series, and of those who initiated, 73.26% completed the series. The RV5 vaccine was administered to 75.71% of infants who initiated the RV vaccine series. The proportion of infants born in each year included in the study were similar, apart from infants born in 2017. Almost 85% of the study population lived in urban areas of the state.

Table 3

Rurality and Rotavirus Vaccine Series Completion-Population Characteristics

Variable	Population (%)	Initiated series (%)	Completed series (%)
Total	293,458	225,541	165,225
Sex			
Female	132,197 (45.05)	108,348 (48.04)	79,998 (48.42)
Male	139,025 (47.38)	113,600 (50.37)	83,455 (50.51)
Race			
Black	118,381 (40.34)	93,025 (41.25)	67,566 (40.89)
Hispanic	26,921 (9.17)	22,402 (9.93)	16,813 (10.18)
Other	20,365 (6.94)	12,030 (5.33)	8,397 (5.08)
White	127,791 (43.55)	98,084 (43.49)	72,449 (43.85)
Vaccine Type			
RV1	---	48,410 (21.46)	40,941 (24.78)
RV5	---	170,750 (75.71)	121,006 (73.24)
Mixed	---	6,381 (2.83)	3,278 (1.98)
Year of Birth			
2010	38,175 (13.01)	29,940 (13.27)	21,574 (13.06)
2011	37,764 (12.87)	30,505 (13.53)	23,308 (14.11)
2012	38,044 (12.96)	30,784 (13.65)	21,916 (13.26)
2013	39,100 (13.32)	31,106 (13.79)	20,780 (12.58)
2014	42,768 (14.57)	31,730 (14.07)	23,154 (14.01)
2015	42,432 (14.46)	31,598 (14.01)	24,037 (14.55)
2016	43,829 (14.94)	32,017 (14.20)	24,448 (14.80)
2017	11,346 (3.87)	7,861 (3.49)	6,008 (3.64)
Residence			
Isolated Rural	8,555 (2.92)	6,750 (2.99)	4,840 (2.93)
Small Rural	13,755 (4.69)	10,971 (4.86)	8,151 (4.93)
Large Rural	22,747 (7.75)	17,585 (7.80)	12,503 (7.57)
Urban	248,401 (84.65)	190,235 (84.35)	139,731 (84.57)

Rotavirus series initiation and rurality. Rotavirus vaccine coverage for at least one vaccination in the RV series was 76.86% in the study population. Rotavirus vaccine coverage for the initiation of the vaccine series by level of rurality and relative risk comparisons of rural-residing infants and urban infants are summarized in Table 4. Coverage for rural locations within the state ranged from 77.31-79.76%. Coverage for at least one RV vaccine among Medicaid-insured infants in urban areas of Alabama was 76.58%. There were statistically significant

differences in relative risk of RV vaccine series initiation between each level of rurality and urban-residing infants. Infants residing in isolated rural (p<.001), small rural towns (p<.001), and large rural towns (p=.0124) were all more likely to initiate the RV vaccine series when compared to infants in urban locations.

Rotavirus series completion and rurality. Rotavirus coverage for the complete RV vaccination series was 56.30% in the study population. Table 4 contains RV vaccine coverage for the completed vaccine series by level of rurality and relative risk comparisons of rural and urban-dwelling infants. Among the Medicaid-insured infants, coverage in rural locations of Alabama ranged from 55.00-59.26%. Urban Medicaid-enrolled infants had a coverage rate of 56.25%. Infants who lived in isolated rural areas (p=.0019) and large rural towns (p<.001) were less likely to complete the RV vaccination series when compared to their urban-dwelling counterparts. There was not a statistically significant difference in series completion between infants in small rural towns and urban infants (p=.0481).

Table 4

Relative Risk of Rotavirus Vaccine Series Initiation & Completion

	Initiation		Completion	
	Coverage	RR [95% CI]	Coverage	RR [95% CI]
Residence				
Isolated Rural	78.90%	1.0303 [1.0188, 1.0418]**	56.58%	0.9762 [0.9614, 0.9912]*
Small Rural	79.76%	1.0415 [1.0325, 1.0506]**	59.26%	1.0115 [1.0001, 1.0230]
Large Rural	77.31%	1.0094 [1.0020, 1.0169]**	54.97%	0.9680 [0.9585, 0.9775]**
Urban	76.58%	---	56.25%	---

*p<.05, **p<.001

Discussion

Infants enrolled in Medicaid were almost equally distributed between sexes, while the demographic information for Medicaid eligibles provided by the Alabama Medicaid Agency (2018) reports the population to be approximately 60% female. This discrepancy is expected, as

Medicaid eligibility extends to disabled and blind adults, impoverished adults over age 65, and pregnant women. Racial composition of the study population is very similar to the demographic breakdown for all Alabama Medicaid eligibles for 2018, in which 42.2% identified as black, 41.5% as white, 5.2% as Hispanic, and 11.1% identified as other (Alabama Medicaid Agency, 2018). A very small number of infants born in 2017 were included in the study population (N=11,346), which was not unexpected due to the inclusion criteria necessary to allow for adequate follow up to capture RV vaccination status.

Healthy People 2020: Immunization and Infectious Diseases Objective 7.10 sets the target coverage for two or more or three or more doses of rotavirus vaccine by age 19 to 35 months at 80.0% (United States Department of Health and Human Services, 2000). The NIS-produced RV vaccine coverage estimate reported by the CDC was 76.2% for the state of Alabama in 2015. Among children living in poverty, the state coverage estimate was 72.0% (Hill, 2016). In the study population of Medicaid-enrolled infants, a substantial proportion of infants who initiated RV vaccination, completed the series (73.26%) according to ACIP-recommended age limits. However, 67,917 infants in the study population did not receive any dose of the RV vaccine series, and only 56.30% of infants in the study population completed the 2-3 dose series. Since current ACIP recommendations do not allow for catch up doses and set a strict age limit for RV vaccine doses at 8 months 0 days of age, it can be inferred that RV vaccine coverage for Medicaid-enrolled infants in Alabama is well below statewide coverage estimates produced by the NIS, as well as the current *Healthy People 2020* target (Cortese & Parashar, 2009).

Rotavirus vaccine coverage among both rural and urban Medicaid-insured infants in Alabama for a minimum of one dose of the series are below the *Healthy People 2020* target of 80% for the full RV vaccine series. Coverage for the complete RV series is approximately 20-25 percentage points lower than the current *Healthy People 2020* target. Coverage for the full RV vaccine series is highest among Medicaid-enrolled infants in small rural towns (59.26%) and isolated rural areas (56.58%) and lowest among residents of large rural towns or micropolitan areas (54.97%) and urban areas (56.25%). Infants in rural areas were significantly more likely than urban infants to initiate the RV vaccine series. Conversely, infants in isolated rural locations and large rural towns or micropolitan areas were less likely to complete the RV vaccine series when compared to urban-dwelling infants. While the differences between rural and urban infants may not be great enough for clinical significance, the finding that rural children were more likely to initiate the RV vaccine series but less likely to complete the series is important. Initiation of the RV vaccine series among rural infants indicates access to health care in early infancy, but decreased likelihood to complete the series may indicate reduced access to preventive health care after the first few months of life. Lower rates of coverage for multiple-dose vaccine series have been found among children living below the poverty level (Hill, 2016; Hill et al., 2015). Decreased access to care among rural children, combined with decreased likelihood for multiple-dose vaccine series completion among children living below the poverty level, may increase RV-disease susceptibility among rural Medicaid-enrolled children.

To better understand causes for decreased completion of the RV vaccine series, examination of other ACIP-recommended vaccinations may be useful. Simultaneous administration of age-appropriate vaccines is particularly important to improve coverage and decrease vaccine-preventable disease. Studies have found a strong correlation between the

number of RV and diphtheria, tetanus, and acellular pertussis (DTaP) vaccine doses received, though RV coverage still lags well behind that for the DTaP vaccine (Panozzo et al., 2013). A recent comparison of RV, DTaP, and pneumococcal conjugate vaccine (PCV) administration found that almost half of infants who did not have a RV vaccination received another ACIP-recommended vaccination between the ages of 6 and 14 weeks, which indicates missed opportunity for simultaneous administration (Pringle et al., 2016). The elimination of missed opportunities for RV vaccination is vital since there is no catch-up schedule for the series and the maximum age for administration of the first RV dose is 14 weeks 6 days (Cortese & Parashar, 2009).

Notably, RV5 vaccines were administered to more than 75% of infants who initiated the RV vaccine series. Studies have indicated that infants are more likely to complete the full RV vaccine series when administered the two-dose RV1 series as compared to the three-dose series required of RV5 (Calnan et al., 2016; Krishnarajah et al., 2012; Krishnarajah et al., 2015). Examination of vaccine type as a predictor of vaccine series completion in the study population should be an area of future study.

There are limitations to the present study. Rotavirus vaccine administration was evaluated via CPT codes in administrative claims data, which are designed for use in billing and reimbursement rather than for research purposes. Medicaid enrollment data was used to assess demographic information and contained self-reported information for sex, race, and location of residence. It is possible that infants changed location of residence in the first 8 months of life. The study population was limited to infants continuously enrolled in the Alabama Medicaid program for eight months after birth. Therefore, results do not reflect vaccination status of

infants with extended lapses in coverage. Furthermore, results may not be applicable to Medicaid-enrolled infants in other states.

Conclusions

There were statistically significant increases in the relative risk of RV vaccine series initiation between isolated rural, small rural town, and large rural town (micropolitan) and urban-residing infants. And though rural infants were more likely to initiate the RV vaccine series, infants in isolated rural areas and large rural towns were less likely to complete the series when compared to urban infants. Regardless of rurality of residence, coverage for the complete RV vaccine series is well below current NIS-produced estimates for the state and the HP2020 target of 80%.

The RV vaccine series is highly effective, with effectiveness improving with each dose in the series (Boom et al., 2010; Donauer et al., 2013; Payne et al., 2013; Payne et al., 2015; Staat et al., 2011). Because low income and rural children are less likely to complete the series, it is important to assess differences between infants who initiate and those who complete the full RV vaccine series. Examination of these differences will allow us to evaluate ways to facilitate completion for those who initiate and to intervene with those who do not.

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ARTICLE 2: PREDICTORS OF ROTAVIRUS VACCINE SERIES COMPLETION IN A MEDICAID POPULATION

Introduction

Worldwide, rotaviruses (RV) infect almost all children by 5 years of age and are the leading cause of severe gastroenteritis among children under age 5 (Centers for Disease Control and Prevention, 2015a; World Health Organization, 2013). Prior to the introduction of the vaccine in the United States, rotaviruses infected an estimated three million Americans and caused 20-60 deaths each year (Centers for Disease Control and Prevention, 2015a; Cortese & Parashar, 2009; Fischer et al., 2007; Glass et al., 1996; Kilgore et al., 1995; Widdowson et al., 2007). Furthermore, gastroenteritis among young children was associated with 55,000-70,000 hospitalizations, 200,000 emergency department visits, and 41,000 outpatient visits, resulting in $1 billion in direct and indirect costs annually (Charles et al., 2006; Cortese & Parashar, 2009; Malek et al., 2006; Parashar et al., 1998; Tucker et al., 1998; Widdowson et al., 2007). Due to the burden of disease caused by rotavirus infection in the United States, the Advisory Committee on Immunization Practices (ACIP) has recommended routine administration of RotaTeq® (RV5) (Merck & Co., Inc.) and Rotarix® (RV1) (GlaxoSmithKline Biologicals) vaccinations since 2006 and 2009, respectively (Cortese & Parashar, 2009; Parashar et al., 2006).

The ACIP recommends routine vaccination of infants, without preference to either currently licensed vaccine. RV5 is to be administered in a three-dose series at 2, 4, and 6 months of age. RV1 is administered as a two-dose series at 2 and 4 months of age. The minimum age for

the first dose of either rotavirus vaccine is 6 weeks 0 days, and all doses should be administered by 8 months 0 days. The minimum acceptable interval between doses is four weeks, and concurrent administration of vaccines for rotavirus, diphtheria, tetanus, and acellular pertussis (DTaP), pneumococcal conjugate vaccine (PCV), *Haemophilus influenzae* type b (Hib), inactivated poliovirus (IPV), and hepatitis B (hep B) is recommended. While completion of the rotavirus vaccine series with the same product is preferred, mixed series are acceptable when administered prior to the maximum age restriction (Centers for Disease Control and Prevention, 2017b; Cortese & Parashar, 2009).

Implementation of the RV vaccine has reduced RV-associated morbidity and healthcare utilization in the United States (Cortes et al., 2011). The Center for Disease Control and Prevention's (CDC) National Respiratory and Enteric Virus Surveillance System (NREVSS) data showed a 57.8-89.9% decrease in RV detection between 2007-2014 (Aliabadi et al., 2015). Post-vaccine, annual epidemics have been replaced by biennial peaks of RV activity, and the onset and peak of seasonal RV activity has been delayed (Pitzer et al., 2009; Tate et al., 2009).

Despite the successful impact of RV vaccines and their inclusion in the schedule of routine childhood immunizations, RV vaccine coverage is among the lowest of all routine childhood vaccinations assessed by the National Immunization Survey (NIS). In 2015, the NIS coverage estimate for two or more or three or more doses of RV vaccine among children aged 19-35 months was 73.2%, well below the *Healthy People 2020* target of 80% (Hill, 2016; United States Department of Health and Human Services, 2000). Only the hepatitis A and hepatitis B (birth dose) vaccines had lower estimated rates of coverage (Hill, 2016). Low coverage rates may result in gaps in local vaccine coverage and a disruption in herd immunity, resulting in the increased risk of RV transmission and outbreaks (Diekema, 2012; Malone & Hinman, 2003; Van

Panhuis et al., 2013). Disparities in vaccination coverage may also contribute to the risk of disease. Historically, Hispanic and non-Hispanic black children, as well as children living below the poverty level, have lower RV coverage rates (Centers for Disease Control and Prevention, 2016b; Hill, 2016; Hill et al., 2015). Furthermore, children enrolled in Medicaid face a disproportionate RV disease burden when compared to privately-insured children (Calnan et al., 2016; Ma et al., 2009).

Lower rates of RV vaccine coverage may be impacted by the recommended childhood immunization schedule, which does not allow for catch-up doses of the RV vaccine series (Centers for Disease Control and Prevention, 2017b; Cortese & Parashar, 2009; United States Department of Health and Human Services). The limited age range of eligibility for vaccination suggests that examination of predictors of RV vaccination may be one avenue for improving lagging coverage rates. Moreover, sociodemographic factors associated with childhood vaccination include race, family income, and geography (region), as well as type of insurance (private, public, or uninsured) (Zhao et al., 2016). Receipt of the DTaP vaccine, completion of the DTaP vaccine series, birth year, receipt of RV1, using a pediatrician as a vaccine provider, and urban residence have been associated with initiation of or completion of the RV series (Calnan et al., 2016; Krishnarajah et al., 2015; Panozzo et al., 2013). And while vaccine effectiveness improves with number of doses received, a reduced risk of RV disease in partially vaccinated children has been observed (Buttery et al., 2011; Curns et al., 2010; Panozzo et al., 2009; Payne et al., 2011). Therefore, the purpose of the present study was to use a health care claims database to examine potential predictors of rotavirus vaccine initiation and series completion in a Medicaid-enrolled infant population.

Methods

Data source. The present study is a retrospective cohort study that utilized an existing database that includes longitudinal claims history, health care provider information, and enrollee eligibility for the Alabama Medicaid program. A monthly average of 580,751 children, 45% of children in the state, with family income below 146% of the Federal Poverty Rate were eligible to enroll in the Alabama Medicaid program during 2016. In 2015, children under age 19 totaled 51% of Alabama Medicaid membership and accounted for 25% of program expenditures (Alabama Medicaid Agency). Analysis was limited to children enrolled between January 1, 2010 through November 30, 2017 due to limitations of the dataset and to ensure adequate follow up for the determination of RV vaccination status.

Study population. The study population was limited to infants born between January 1, 2010 and March 1, 2017 who were continuously enrolled in Medicaid for at least eight months following birth. Continuous enrollment is defined as enrollment every month from birth to age 8 months 0 days, the maximum age for receipt of a RV vaccine dose. The requirement of continuous enrollment allowed for analysis of health care encounters when RV vaccines were administered. A 30-day gap in eligibility immediately following birth was acceptable, as newborn enrollment in Medicaid may be delayed. Because of inadequate time for follow up, infants born after March 1, 2017 were excluded from analysis. Infants who received any dose of RV vaccine prior to age 6 weeks 0 days, the minimum age for RV vaccination as recommended by the ACIP, were excluded from the analysis.

Predictors. Predictors of interest for RV vaccine initiation and series completion that identified in the literature and available in the data included sex, race, year of birth, rural/urban residence, RV vaccine type, vaccination provider specialty, and receipt of diphtheria, tetanus

toxoids, and acellular pertussis (DTaP) vaccine. Sex and race for enrolled children was available in the Medicaid administrative claims data. Analysis was limited to enrolled children identified as white, black, Hispanic, or other. Type of RV vaccine was categorized by CPT code: RV5 as indicated by a claim of 90680, RV1 as indicated by 90681, and mixed for infants with claims for both 90680 and 90681 (American Academy of Pediatrics, 2016). DTaP vaccination initiation was an indicator of whether each infant received any DTaP vaccination prior to 8 months of age, and DTaP series completion was an indicator of the receipt of three DTaP doses by 8 months 0 days of age. Rurality of residence was defined using zip code approximations of Rural Urban Commuting Area (RUCA) codes and condensed using categorization A: Urban focused, large rural city/town focused (Micropolitan), small rural town focused, and isolated small rural town focused (Rural Health Research Center, 2007; United States Department of Agriculture, 2016).

Other predictors of interest included provider specialty, practice type, and the use of the same type immunization providers. Previous studies have found that the receipt of routine care from a pediatrician increases likelihood of RV series completion (Krishnarajah et al., 2012; Panozzo et al., 2013). Provider specialty was collapsed into pediatric specialty or other. NIS-produced coverages estimates for the Rotavirus vaccine among children aged 19-35 months indicate that private providers have higher coverage rates than public vaccination providers (Centers for Disease Control and Prevention, 2015b). Practice type was dichotomized into individual or physician group practices (private provider) or other (public health clinics, community health centers, hospitals, urgent care facilities). Concordant provider was an indicator of whether doses in the RV vaccine series were administered by providers of the same or different specialties in the analysis of RV vaccine series completion.

Outcome measures. Rotavirus vaccine initiation is defined as the receipt of ≥1 dose of either RV5 (90680) or RV1 (90681) prior to 14 weeks 6 days of age, the ACIP-recommended maximum age for the first dose of RV vaccine (yes/no) (American Academy of Pediatrics, 2016). Completion of the RV vaccination series is defined as the receipt of three doses of RV5, two doses of RV1, or two doses of RV5 and one dose of RV1 (any order) by 8 months 0 days of age, in accordance with current ACIP recommendations (yes/no).

Statistical analyses. Frequencies and proportions were used to summarize demographic characteristics and categorical predictors for the study population and by RV vaccination status. A multivariate modified Poisson regression using a log link function was used to analyze relative risks between potential predictors and the binary outcome variables, RV series initiation and RV series completion. Relative risk is preferred over computation of an odds ratio when the probability of an outcome is high (Zou, 2004). Standard error for relative risk is overestimated when Poisson regression is applied to a binary outcome variable; therefore, the modified Poisson uses a robust error variance to estimate standard errors for relative risk (Greenland, 2004; Spiegelman & Hertzmark, 2005; Zou, 2004). Relative risk and 95% confidence intervals for predictors are presented. The LSMEANS statement was utilized to obtain relative risk estimates (SAS, 2002, 2004). The data analysis for this paper was generated using SAS software.

Results

Population characteristics. A total of 293,458 infants were included in the study population. Characteristics of the total population and characteristics by RV series completion are presented in Table 5. Almost 77% of infants in the study population (*N*=225,541) initiated

the RV vaccine series by the ACIP-recommended maximum age for administration of the first dose of 14 weeks 6 days of age. A total of 165,225 infants (56.30%) from the study population completed the RV series prior to 8 months 0 days of age. The population was almost 85% urban, 40% Black, and 41% White, with very similar numbers of male and female infants. Eighty-four percent of the infant population had received at least one DTaP dose, while only 63% had received 3 or more DTaP doses, which would indicate compliance with ACIP recommendations for the administration of the vaccine (Centers for Disease Control and Prevention, 2017b).

Table 5

Predictors of Rotavirus Vaccine Series Completion-Population Characteristics

Variable	Population (%)	Initiated Series (%)	Completed Series (%)
Total	293,458	225,541	165,225
Sex			
Female	132,197 (45.05)	108,348 (48.04)	79,998 (48.42)
Male	139,025 (47.38)	113,600 (50.37)	83,455 (50.51)
Race			
Black	118,381 (40.34)	93,025 (41.25)	67,566 (40.89)
Hispanic	26,921 (9.17)	22,402 (9.93)	16,813 (10.18)
Other	20,365 (6.94)	12,030 (5.33)	8,397 (5.08)
White	127,791 (43.55)	98,084 (43.49)	72,449 (43.85)
Residence			
Isolated Rural	8,555 (2.92)	6,750 (2.99)	4,840 (2.93)
Small Rural	13,755 (4.69)	10,971 (4.86)	8,151 (4.93)
Large Rural	22,747 (7.75)	17,585 (7.80)	12,503 (7.57)
Urban	248,401 (84.65)	190,235 (84.35)	139,731 (84.57)
Provider Type			
Pediatric	---	136,220 (60.40)	102,366 (61.96)
Other	---	89,321 (39.60)	62,859 (38.04)
Practice Type			
Individual	---	163,572 (72.52)	119,816 (72.52)
Other	---	61,969 (27.48)	45,409 (27.48)
DTaP (≥1 dose)			
Yes	247,207 (84.24)	225,107 (99.81)	---
No	46,251 (15.76)	434 (0.19)	---
Concordant Provider			
Yes	---	---	140,925 (85.29)
No	---	---	24,300 (14.71)
DTaP (≥3 doses)			
Yes	184,001 (62.70)	---	158,065 (95.67)
No	109,457 (37.30)	---	7,160 (4.33)
Vaccine Type			
Mixed	---	---	3,278 (1.98)
RV1	---	---	40,941 (24.78)
RV5	---	---	121,006 (73.24)

Note. Column percentages are presented.

Rotavirus vaccine series initiation. Of the 225,541 infants who initiated the RV vaccine series, 60.40% had received their vaccine doses from a General Pediatrician or Pediatric Nurse Practitioner. Furthermore, 72.52% had doses administered at an individual or group physician practice. Notably, 99.8% of infants who received at least one RV vaccine dose had also received at least one dose of the DTaP vaccine series by 8 months of age.

Results for the multivariate analysis of predictors of RV vaccine series initiation are presented in Table 6. Infants who initiated the DTaP series were 53.02 times as likely to initiate the RV vaccine series as those who did not receive at least one DTaP dose in infancy ($p<.001$). Significant differences in risk were also found by practice type, physician specialty, race, and rurality of residence. Infants seen at individual or group physician practices were 1.16 times as likely initiate the series when compared to those seen at public health clinics, community health centers or urgency care facilities ($p<.001$). Furthermore, infants seen by Pediatricians or Pediatric Nurse Practitioners were 1.03 times as likely to initiate the RV series when compared to those seen by providers of other specialties ($p<.001$). When compared to white infants, Hispanic infants were significantly more likely to initiate the RV series ($p<.001$). There was no significant difference between white and black infants ($p=.1292$). Rural infants were significantly more likely to initiate the RV series when compared to Urban infants. There was no significant difference in risk of RV vaccine series initiation between female and male infants ($p=.2240$).

Table 6

Relative Risk of Rotavirus Vaccine Series Initiation and Completion

Variable	Initiated RV Series		Completed RV Series	
	RR	95% CI	RR	95% CI
Sex				
Female	1.0015	[0.9991, 1.0039]	1.0003	[0.9968, 1.0039]
Male	---	---	---	---
Race				
Black	0.9980	[0.9953, 1.0006]	0.9935*	[0.9897, 0.9974]
Hispanic	1.0286**	[1.0247, 1.0326]	0.9853**	[0.9792, 0.9915]
Other	0.9179**	[0.9113, 0.9246]	0.9832**	[0.9748, 0.9918]
White	---	---	---	---
Residence				
Isolated Rural	1.0107*	[1.0032, 1.0182]	0.9810**	[0.9702, 0.9919]
Small Rural	1.0259**	[1.0201, 1.0317]	1.0267**	[1.0187, 1.0347]
Large Rural	1.0190**	[1.0145, 1.0236]	0.9973	[0.9904, 1.0043]
Urban	---	---	---	---
Provider Type				
Pediatric	1.0331**	[1.0297, 1.0366]	1.0738**	[1.0667, 1.0810]
Other	---	---	---	---
Practice Type				
Individual	1.1622**	[1.1566, 1.1678]	0.9408**	[0.9333, 0.9483]
Other	---	---	---	---
DTaP (≥1 dose)				
Yes	53.0228**	[48.2162, 58.3086]	---	---
No	---	---	---	---
Concordant Provider				
Yes	---	---	0.9901*	[0.9836, 0.9967]
No	---	---	---	---
DTaP (≥3 doses)				
Yes	---	---	4.1127**	[4.0298, 4.1973]
No	---	---	---	---
Vaccine Type				
Mixed			1.1587**	[1.1503, 1.1672]
RV1			1.1962**	[1.1911, 1.2014]
RV5			---	---

Note. Reference categories are italicized. *p<.01, **p<.001

Rotavirus vaccine series completion. The proportion of infants who completed the RV series who were seen by a pediatric practitioner (61.96%) and in individual or group practices (72.52%) was similar to the result for series initiation. Approximately 85% of infants who completed the series received RV vaccine doses from providers of the same specialty, and almost 97% had received 3 or more age-appropriate doses of the DTaP vaccine series. The RV5 vaccine was administered to the majority of infants (73.24%) who completed the series.

Table 6 presents results of the multivariate analysis for predictors for RV series completion. Infants who had received three or more DTaP doses were 4.11 times as likely to complete the RV vaccine series as those infants who had not received all age-appropriate DTaP doses ($p<.001$). Infants who were administered mixed type doses were 1.16 times as likely and those administered RV1 were 1.20 times as likely to complete the series when compared to infants administered the RV5 vaccine ($p<.001$). Infants who received doses of the RV series from Pediatricians or Pediatric Nurse practitioners were 1.07 times as likely to complete the series when compared to infants seen by providers of other specialties ($p<.001$).

Unlike risk of RV series initiation, infants who received vaccination doses from physicians in individual or group practice were slightly less likely to complete the series when compared to infants who received RV vaccine doses at public health clinics, community health centers, or urgent care facilities ($p<.001$). Infants who received doses from providers of the same specialty (concordant providers) were also less likely to complete the RV vaccine series ($p=0.0034$). When compared to urban infants, infants in isolated rural areas were less likely to complete the series ($p=0.006$), but those in small rural towns were more likely to complete the series ($p<.001$). There was no significant difference in completion between infants in large rural (micropolitan) towns and those in urban areas ($p=0.4526$). All racial groups were significantly

less likely to complete the series when compared to white infants. As with the results for risk of initiation, there was no significant difference in risk of RV vaccine series completion between females and males (p=0.8263).

Discussion

In the present study of Medicaid-enrolled infants from 2010-2017, a sizeable proportion of infants initiated the RV vaccine series (76.86%). Among Medicaid-enrolled children, Krishnarajah et al. (2015) found receipt of the initial RV vaccine dose increased the likelihood of receipt of subsequent doses. Similarly, the present study found that 73.26% of infants who received at least dose of RV vaccine prior to the first dose upper age limit (initiated the series), completed the RV vaccine series prior to age 8 months 0 days. The proportion of infants who did not receive any doses of RV vaccine (23.14%) was considerably lower than was found in similar studies of Medicaid-enrolled infants (Calnan et al., 2016; Krishnarajah et al., 2015).

Additionally, results from the present study found that completion of the RV vaccine series (56.30%) to be less than current CDC-reported coverage estimates. The National Immunization Survey (NIS)-produced RV vaccine coverage estimate for the complete RV series among children aged 19 to 35 months in Alabama was 76.2% (Hill, 2016). The NIS estimates population vaccine coverage for children aged 19 to 35 months and does not provide estimates by insurance status (Centers for Disease Control and Prevention, 2016a; Panozzo et al., 2013). It is reasonable to compare the coverage rate found in the present study to NIS-produced estimates because of the strict upper age limit and absence of catch-up doses in the ACIP recommendations for RV vaccine administration, and the rate of completion is based on the entire population of age-eligible children rather than the proportion of infants who initiated the RV series (Krishnarajah et al., 2012). Uninsured children and Medicaid-enrolled children are less

likely to be vaccinated when compared to their commercially-insured counterparts (Panozzo et al., 2013). When limited to children living below the federal poverty level, the NIS-produced RV coverage estimate for Alabama decreased to 72.0%, which is 15.7 percentage points higher than the coverage rate of 56.30% found in our study population. (Hill et al., 2015).

Furthermore, the strongest predictor for RV series initiation and completion was receipt of ≥1 dose of DTaP vaccine and receipt of ≥3 doses of DTaP vaccine, respectively. These findings support findings from similar studies of the predictors of RV vaccination in Medicaid and commercially-insured children (Krishnarajah et al., 2015; Panozzo et al., 2013). The magnitude of the association between RV vaccine series initiation and the receipt of at least one dose DTaP vaccine may indicate provider adherence to the ACIP recommendation of simultaneous administration of age-appropriate vaccinations. Although the association between the receipt of ≥3 doses of DTaP vaccine and RV vaccine series completion is also very strong, the proportion of infants that completed age-appropriate doses of both vaccines are dissimilar. The proportion of the study population that had received of 3 or more DTaP doses by 8 months of age was 62.70%, while only 56.30% of the population completed the required RV vaccine doses during the same time age range. Studies have shown that increasing the coverage rate of one childhood vaccination results in the increase in coverage to other recommended vaccines (Calnan et al., 2016; Hull et al., 2013; Panozzo et al., 2013; Wendy, 2012). However, the discrepancy in completion rates for the RV vaccine series and age-appropriate DTaP doses in the study population suggests the importance of other predictors in improving RV vaccine coverage among Medicaid-insured infants.

Vaccine type is also an important predictor of RV vaccine series completion in this population of Medicaid-enrolled infants. Previous studies have found that infants who were administered the RV1 rotavirus vaccine were more likely to complete the series when compared to infants who were administered RV5 (Krishnarajah et al., 2012; Krishnarajah et al., 2015; Panozzo et al., 2013). Results from the present study further support these findings. Among infants who received only doses of RV5, 70.87% completed the series, while almost 85% of infants who received only RV1 doses completed the series. Although the majority of infants in the study population received RV5 doses, infants who received RV1 were more likely to complete the series. Calnan et al. (2015) found decreased compliance for each successive dose in both the RV1 and RV5 vaccine series. Since infants who receive the RV5 vaccine are required to receive three doses, as opposed to two doses required of RV1, it seems reasonable that there is an increased risk of completion among infants who received only RV1 doses.

Finally, other notable predictors of RV vaccination included provider specialty, rurality of residence, and race. Receipt of RV doses from a Pediatric provider increased the likelihood of both series initiation and completion in the present study. Studies that have compared RV vaccination between Pediatricians and Family Medicine physicians also found that Pediatricians were more compliant to ACIP-recommendations for RV vaccine administration and that the receipt of routine medical care from a Pediatrician increased the likelihood of series completion (Calnan et al., 2016; Panozzo et al., 2013). The literature concerning RV completion and rurality of residence has produced mixed results. Panozzo et al. (2013) reports that children who lived in non-metropolitan areas were less likely to complete the RV vaccine series. Estimates produced using the NIS have revealed differences in Rotavirus coverage rates by race and urbanicity. Children living in Non- Metropolitan Statistical Areas (MSA) had lower coverage than their

urban counterparts; however, children in MSA Non Central Cities had the highest rates of coverage (Hill, 2016; Hill et al., 2015). The present study also found mixed results. Infants in remote rural locations and large rural towns or micropolitan areas were less likely to complete the RV vaccine series when compared to urban-dwelling infants; whereas infants in small rural town were more likely than urban infants to complete the series. The results for racial differences in RV series completion supported findings in the literature, which found that Hispanic and black children had lower coverage when compared to non-Hispanic white children (Centers for Disease Control and Prevention, 2015b; Hill, 2016; Hill et al., 2015).

When considering the present study, there are limitations. The study relied on administrative claims data, which are designed for use in billing and reimbursement rather than for research purposes. Claims data, rather than a medical record, was used to locate CPT codes for RV vaccine administration. Medicaid enrollment data was used to assess demographic information and contained self-reported information for sex, race, and location of residence. The study population was limited to infants in the Alabama Medicaid program. Therefore, study results are not representative of uninsured or commercially insured infants and may not be applicable to Medicaid-enrolled infants in other states.

Conclusions

A substantial proportion of Medicaid-enrolled infant in Alabama initiated the RV vaccine series. However, the proportion of infants who completed the series by the ACIP-recommended upper age limit was considerably lower than current coverage estimates for the state and the *Healthy People 2020* target of 80% (United States Department of Health and Human Services, 2000). The most important predictor of RV vaccine series initiation was the receipt of at least one DTaP dose. Moreover, receipt of all age-appropriate DTaP doses (≥3) and receipt of the

RV1 vaccine were the strongest predictors of RV vaccine series completion in the study population. The achievement of RV vaccine coverage targets continues to be a challenge. It is evident that receipt of a partial RV series is achievable by a considerable proportion of infants. Thus, further analysis of health outcomes by degree of RV vaccine series completion is timely.

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ARTICLE 3: ROTAVIRUS VACCINE SERIES COMPLETION AND HEALTH CARE UTILIZATION IN A MEDICAID POPULATION

Introduction

Rotaviruses are the leading cause of severe gastroenteritis in young children, infecting almost all children by age 5 (Centers for Disease Control and Prevention, 2015a; World Health Organization, 2013). Although, 20-60 deaths annually were attributed to rotavirus, it was estimated that three million RV infections occurred each year in the United States prior to RV vaccine licensure (Centers for Disease Control and Prevention, 2015a; Cortese & Parashar, 2009; Fischer et al., 2007; Glass et al., 1996; Kilgore et al., 1995; Widdowson et al., 2007). Active surveillance found that rotavirus (RV) was the cause for a significant proportion of child hospitalizations, emergency department visits, and outpatient visits for acute gastroenteritis (AGE) (Mast et al., 2010). Annual direct and indirect costs attributed to RV totaled approximately $1 billion, which was a result of 55,000 to 70,000 hospitalizations, 205,000 to 272,000 emergency department visits, and 410,000 outpatient visits pre-vaccine (Charles et al., 2006; Cortese & Parashar, 2009; Malek et al., 2006; Parashar et al., 1998; Tucker et al., 1998).

Rotavirus vaccines, RotaTeq® (RV5) (Merck & Co., Inc.) and Rotarix® (RV1) (GlaxoSmithKline Biologicals), have been recommended for routine use in the United States by the Advisory Committee on Immunization Practices (ACIP) since 2006 and 2009, respectively (Cortese & Parashar, 2009; Parashar et al., 2006). RV5 is administered as a three-dose series at 2, 4, and 6 months of age. RV1 is a two-dose series to be administered at 2 and 4 months of age. The first RV vaccine dose should not be administered before age 6 weeks 0 days, and no dose

should be given after age 8 months 0 days. A minimum interval of four weeks is required between doses, and, although not preferred, vaccine type may be mixed during the RV vaccine series. Simultaneous administration is acceptable and an important consideration as other routine childhood vaccinations are recommended during similar age rages (Centers for Disease Control and Prevention, 2013a; Cortese & Parashar, 2009). Coverage estimates produced by the Centers for Disease Control and Prevention (CDC) using data from the 2015 National Immunization Survey (NIS) indicate that only 73.2% of children aged 19-35 months had completed the full RV vaccine series (Hill, 2016).

The introduction of rotavirus vaccines into the schedule of routine childhood immunizations resulted in significant decreases in RV-associated illness and health care utilization. National surveillance found a 57.8%-89.9% decrease in RV detection from 2007-2014 (Aliabadi et al., 2015). When compared to costs prior to vaccine introduction (Kilgore et al., 2013), 2006-2009 data from the New Vaccine Surveillance Network revealed an annual reduction in medical costs for laboratory-confirmed RV hospitalizations and emergency department visits of $187 million (Kilgore et al., 2013). Although vaccine effectiveness is maximized with the full RV series, post-licensure studies have found that partial and complete RV vaccine series are highly effective against severe RV disease (Boom et al., 2010; Desai et al., 2010; Donauer et al., 2013; Payne et al., 2013; Payne et al., 2015; Staat et al., 2011).

Furthermore, NIS coverage estimates reveal that completion of the RV series lags behind other routine childhood vaccinations, which makes the examination of RV disease and health care utilization among partially vaccinated children relevant and timely (Cortese & Parashar, 2009; Hill, 2016). Rates of RV vaccine series completion vary widely from study to study. Analysis of a Medicaid-insured population found that between 47%-52% of children had

completed the series per ACIP recommendations (Calnan et al., 2016). A separate study of Medicaid-insured children found that only 32.6% were completely vaccinated and over 40.0% had not received any RV vaccine dose (Krishnarajah et al., 2015). Krishnarajah et al. (2012) assessed series completion in commercially-insured children and found completion rates ranging from 67.5%-91.0%, depending upon product that was used for the series. In a more recent study, Krishnarajah et al (2016) assessed the clinical and economic impact of RV vaccination among children under age 5. Results showed the incidence of RV infection was more than five times higher among commercially-insured and two times higher among Medicaid-insured children who were unvaccinated, when compared to their completely vaccinated counterparts. Rotavirus incidence among unvaccinated children was also significantly higher than both incompletely vaccinated commercially-insured and Medicaid-insured children. Moreover, when compared to completely or incompletely vaccinated children, rotavirus-associated health care costs in both commercially-insured and Medicaid-insured children were significantly higher among unvaccinated children. However, this study did not compare RV incidence or costs between completely and incompletely vaccinated children, which a comparison of interest because the same study found that only 43.8% of the commercially-insured children and 12.9% of the Medicaid-insured children had completed the RV series according to ACIP guidelines (Krishnarajah et al., 2016).

As fewer Medicaid-insured children complete the RV vaccine series, while facing higher RV disease burden and health care utilization than commercially-insured children, examination of the effectiveness of partial RV vaccine series completion is important. Therefore, the purpose of the present study is to compare health care utilization and cost among Medicaid-insured children by status of RV vaccine series completion.

Methods

Data source. The present study is a retrospective cohort study that utilized Alabama Medicaid program administrative claims database that includes eligibility, demographic, and healthcare service utilization information for Medicaid enrollees. In 2016, a monthly average of 580,751 children, representing 45% of the children in Alabama, were eligible to enroll in the state's Medicaid program. Analysis was limited to data from children enrolled from January 1, 2010 through December 31, 2017.

Study population. The study population included infants born between January 1, 2010 and May 1, 2017 and continuously enrolled in the state Medicaid program for at least eight months following birth. Continuous enrollment was defined as enrollment every month from birth to age 8 months 0 days to ensure capture of rotavirus vaccination encounters. Infants with a 30-day gap in eligibility immediately following birth were included in the study. Infants born after April 1, 2017 were excluded from the present study due to inadequate time for follow up. Infants who received any dose of RV vaccine prior to the ACIP-recommended minimum age for first RV vaccine dose of age 6 weeks 0 days were excluded from the analysis. Claims data from eligible children were analyzed from birth to the end of continuous eligibility or 5 years of age.

Measure of rotavirus vaccine series completion. Receipt of a RV vaccine was identified by Current Procedural Terminology (CPT) codes 90680 (RV5) and 90681 (RV1) (American Academy of Pediatrics, 2016). Level of RV series completion was determined using ACIP dosing recommendations. Completion of the rotavirus vaccine series was defined infants who received three doses of RV5, two doses of RV1, or three doses of RV1/RV5 (mixed) by age 8 months 0 days. A partial series is defined as infants who received one to two doses of RV5, one dose of RV1, or one to two doses of RV1/RV5 (mixed) by age 8 months, but did not

complete the full RV series. Unvaccinated infants have no record of the receipt of either RV5 or RV1 vaccination by age 8 months 0 days after date of birth.

Measures of health care utilization. Clinical outcomes included RV and diarrhea-coded hospitalizations (inpatient facilities), emergency department visits, and outpatient visits (includes outpatient urgent care facilities). Location of health care utilization was determined by place of service as recorded in the Medicaid database. The identification of RV and diarrhea-associated health care utilization was assessed using International Classification of Diseases (ICD) codes. The transition from the International Classification of Diseases, Ninth Revision (ICD-9) and the International Classification of Diseases, Tenth Edition (ICD-10) occurred in 2015. For healthcare claims dated prior to October 1, 2015, ICD-9 codes for rotavirus and nonspecific diarrhea will be identified and used in the analysis of healthcare utilization by RV vaccine series completion. Claims dated October 1, 2015 through November 30, 2017 will be identified using ICD-10 codes for rotavirus and nonspecific diarrhea (Centers for Medicare and Medicaid Services, 2018; World Health Organization, 1978, 2004).

RV-coded encounters were identified as one of the primary or secondary diagnoses by the specific ICD-9 (008.61) and ICD-10 (A08.0) code for RV (Centers for Medicare and Medicaid Services, 2014, 2015). Testing for RV is not routine, and the RV-specific diagnosis code in hospital discharge data and claims data underestimates the impact of RV (Hsu et al., 2005; Mast et al., 2010). As a result, ICD codes for nonspecific diarrhea as one of the primary or secondary diagnoses were used to assess diarrhea-coded healthcare utilization (Cortes et al., 2011; Krishnarajah et al., 2016). ICD-9 codes used for analysis and the corresponding ICD-10 codes are found in the appendix.

Economic outcomes included cost of RV-coded and diarrhea-coded healthcare utilization. Mean cost of RV-coded and nonspecific-diarrhea-coded hospitalizations, emergency department, and outpatient were calculated for each level of RV vaccine series completion. Analysis was limited to first bout of RV-coded and nonspecific-diarrhea-coded illness for each enrolled child. An single bout of illness was assumed to last from 14 days before the first RV or nonspecific-diarrhea-coded encounter to 14 days after the last RV or nonspecific-diarrhea-coded encounter (Cortes et al., 2011; Krishnarajah et al., 2016).

Statistical analysis. Frequencies and proportions for population characteristics are reported. Incidence rates were calculated by dividing number of RV-coded and diarrhea-coded encounters by the person-time (months) of observation in each level of RV vaccine series completion. Medicaid enrollment is assessed each month, therefore, person-time for incidence rates was calculated as person-months. Analysis was limited to the first bout of RV-coded and nonspecific-diarrhea-coded illness for each enrolled infant within each provider setting. Incidence rate ratios (IRR) and 95% confidence intervals were generated via Poisson regressions and were used to compare incidence of RV-coded and nonspecific-diarrhea-coded hospitalizations, ED visits, and outpatient visits by level of RV vaccine series completion. The Poisson model was used for the ability to model counts and individual or grouped counts. The model was addressed the necessity to account for varied lengths of follow up between levels of RV vaccine series completion, which was accomplished by the inclusion of the person-time variable as an offset of the outcome variable (Coxe, West, & Aiken, 2009; Hutchinson & Holtman, 2005; Rodriguez, 2007).

Measures of normality were completed for cost variables. Both mean and median cost of RV-coded and nonspecific-diarrhea-coded hospitalizations, emergency department, and

outpatient visits were calculated within each level of vaccine series completion. Although cost data is often not normally distributed, discussion of mean cost is often appropriate in descriptions of health care utilization (Nixon & Thompson, 2004). Because costs for RV-coded cases of illness were not normally distributed, medians were used for comparison between levels of RV vaccine series completion. Differences in the median cost for RV-coded and nonspecific-diarrhea-coded healthcare utilization by RV vaccination status were analyzed using Kruskal-Wallis tests (Kilgore et al., 2013). Costs were adjusted to 2017 U.S. dollars using the medical care component of the Consumer Price Index. The data analysis for this paper was generated using SAS software.

Results

A total of 293,407 children in our study population accumulated 9,640,094 person-months of observation. Mean months of observation for completely vaccinated children in our study population was 36.0 months, 34.9 months among partially vaccinated children, and 23.5 months among unvaccinated children. Population characteristics are presented in Table 7. Approximately 23% of the population had received no RV vaccine doses by 8 months 0 days of age. An additional 20.55% had only completed a partial RV vaccine series. Only 165,198 infants (56.30%) completed the full RV vaccine series by the ACIP-recommended age limit.

Table 7

Rotavirus Vaccine Series Completion and Health Care Utilization-Population Characteristics

Variable	Total population	Unvaccinated (%)	Partially vaccinated (%)	Completely vaccinated (%)
	293,407	67,906 (23.14)	60,303 (20.55)	165,198 (56.30)
Sex				
Female	132,173	23,842 (18.04)	28,344 (21.44)	79,987 (60.52)
Male	138,999	25,421 (18.29)	30,139 (21.68)	83,439 (60.03)
Race				
Black	118,363	25,351 (21.42)	25,454 (21.51)	67,558 (57.08)
Hispanic	26,918	4,519 (16.79)	5,587 (20.76)	16,812 (62.46)
Other	20,362	8,333 (40.92)	3,632 (17.84)	8,397 (41.24)
White	127,764	29,703 (23.25)	25,630 (20.06)	72,431 (56.69)
Year of Birth				
2010	38,159	8,233 (21.58)	8,363 (21.92)	21,563 (56.51)
2011	37,760	7,258 (19.22)	7,195 (19.05)	23,307 (61.72)
2012	38,039	7,259 (19.08)	8,865 (23.31)	21,915 (57.61)
2013	39,093	7,993 (20.45)	10,324 (26.41)	20,776 (53.15)
2014	42,763	11,037 (25.81)	8,573 (20.05)	23,153 (54.14)
2015	42,425	10,830 (25.53)	7,561 (17.82)	24,034 (56.65)
2016	43,822	11,811 (26.95)	7,569 (17.27)	24,442 (55.78)
2017	11,346	3,485 (30.72)	1,853 (16.33)	6,008 (52.95)
Residence				
Isolated Rural	8,550	1,804 (21.10)	1,909 (22.33)	4,837 (56.57)
Small Rural	13,754	2,784 (20.24)	2,820 (20.50)	8,150 (59.26)
Large Rural	22,740	5,162 (22.70)	5,079 (22.34)	12,499 (54.96)
Urban	248,863	58,156 (23.37)	50,495 (20.29)	139,712 (56.14)
Vaccine Type				
RV5	170,717	---	49,731 (29.13)	120,986 (70.87)
RV1	48,403	---	7,469 (15.43)	40,934 (84.57)
Mixed	6,381	---	3,103 (48.63)	3,278 (51.37)

Rotavirus-coded illness and health care utilization. A total of 400 cases of RV-coded illness occurred in Medicaid-enrolled children under age 5 from 2010-2017. Of these, 45.75% were hospitalized, 39.00% were treated as outpatients, and 15.25% were treated in emergency departments. Of the 400 RV-coded cases of illness, 210 were among children completely vaccinated against RV, 95 cases were found among partially vaccinated children, and an additional 95 cases occurred among children who had not received any RV vaccine doses.

Incidence rates and incidence ratios for RV-coded cases of illness by provider type and RV vaccine series status are presented in Table 8. The incidence rate of RV-coded hospitalizations among children who had received the complete RV vaccination series was significantly lower than the rates for both partially vaccinated and vaccinated children. Furthermore, the rate for partially vaccinated children was significantly lower than that for unvaccinated children in the study population. The incidence rate of RV-coded hospitalizations among unvaccinated children was 2.52 times higher than the rate for children who completed the full RV vaccine series and 1.68 times higher than children who had completed a partial RV series. Partially vaccinated children had an incidence rate of RV-coded hospitalizations that was 1.50 times higher than that for complete vaccinated children. Furthermore, incidence of RV illness that required an emergency department visit was significantly lower among completely vaccinated children, when compared to partially vaccinated and unvaccinated children. When compared to children who had completed the RV vaccine series, the incidence rate of RV-coded ED visits was 1.94 times higher among unvaccinated and 2.10 times higher among partially vaccinated children. There were no significant differences in incidence of RV-coded outpatient visits between the levels of RV vaccine series completion.

Table 8

Incidence of Rotavirus-Coded Health Care Utilization (per 100,000 persons per month)

	Incidence		IRR [95% CI]
	Complete Series	Unvaccinated	
Hospitalizations	1.40	3.52	0.3971*** [0.2829, 0.5573]
ED Visits	0.45	0.88	0.5167* [0.2709, 0.9853]
Outpatient Visits	1.68	1.57	1.0716 [0.6914, 1.6610]
	Partial Series	Unvaccinated	
Hospitalizations	2.09	3.52	0.5949** [0.4008, 0.8829]
ED Visits	0.95	0.88	1.0816 [0.5463, 2.1412]
Outpatient Visits	1.47	1.57	0.9388 [0.5543, 1.5899]
	Complete Series	Partial Series	
Hospitalizations	1.40	2.09	0.6675* [0.4632, 0.9620]
ED Visits	0.45	0.95	0.4777* [0.2679, 0.8517]
Outpatient Visits	1.68	1.47	1.1415 [0.7629, 1.7078]

*p<.05, **p<.01, ***p<.001

The mean cost of RV-coded hospitalizations ($4,337.75) was highest among children who had complete the full RV vaccine series and lowest among unvaccinated children ($3,925.87). Mean cost of treatment for RV-coded emergency department ($174.31) and outpatient visits ($130.49) were highest among partially vaccinated children. Cases of illness, as well as mean and median cost of RV-coded health care encounters by RV vaccine series completion, are presented in Table 9. There were no significant differences in median cost of treatment for RV-coded illness by vaccine series status for any of the healthcare provider categories.

Table 9

Cost of Rotavirus-Coded Health Care Utilization

	RV Series Status	*N*	Mean	Median	IQR	*p*-value
Hospitalizations	Unvaccinated	56	3,925.87	3,404.68	2,069.58-5,223.94	0.9158
	Partially Vaccinated	44	4,067.29	3,112.34	2,120.04-5,684.94	
	Completely Vaccinated	83	4,337.75	3,234.81	1,246.27-5,776.12	
Emergency Department Visits	Unvaccinated	14	117.53	111.89	87.64-148.75	0.1147
	Partially Vaccinated	20	174.31	135.44	108.54-237.60	
	Completely Vaccinated	27	141.19	89.02	44.38-188.26	
Outpatient Visits	Unvaccinated	25	94.71	116.62	48.80-134.20	0.0773
	Partially Vaccinated	31	130.49	134.20	81.17-168.98	
	Completely Vaccinated	100	117.25	130.90	69.56-134.20	

Note. Mean, median, and interquartile range (IQR) values in $2017.

Nonspecific-diarrhea-coded illness and health care utilization. From 2010-2017, there were 111,026 cases of nonspecific-diarrhea-coded illness among Medicaid-enrolled children younger than five years of age. The majority of cases (66.28%) were treated as outpatients. Almost 30% of nonspecific-diarrhea-coded cases of illness were treated in emergency departments, and fewer than 5% required hospitalization. Sixty-six percent of the cases of nonspecific-diarrhea-coded illness occurred among children who were completely vaccinated against RV disease.

Incidence rates and incidence ratios for nonspecific-diarrhea-coded cases of illness by provider type and RV vaccine series status are reported in Table 10. Incidence rates of nonspecific-diarrhea-coded hospitalizations of children who had completed the full RV vaccine series were significantly lower than for partially vaccinated or unvaccinated children. Compared to children who had completed the full RV vaccine series, incidence rates of nonspecific-diarrhea-coded hospitalizations were 1.17 times and 1.10 times higher among unvaccinated and partially vaccinated children, respectively. Incidence of nonspecific-diarrhea-coded illness emergency department and outpatient visits among unvaccinated children were significantly lower than the rates for both partially or completely vaccinated children. The incidence rate of diarrhea-coded outpatient visits was 1.58 times higher among completely vaccinated and 1.37 times higher among partially vaccinated children when compared to the rate for unvaccinated children.

Table 10

Incidence of Nonspecific-Diarrhea-Coded Health Care Utilization (per 100,000 persons per month)

	Incidence		IRR (95% CI)
	Completely Vaccinated	Unvaccinated	
Hospitalizations	46.65	54.56	0.8549** [0.7922, 0.9226]
ED Visits	346.19	307.86	1.1245** [1.0900, 1.1601]
Outpatient Visits	839.05	530.70	1.5810** [1.5450, 1.6179]
	Partially Vaccinated	Unvaccinated	
Hospitalizations	51.44	54.56	0.9427 [0.8622, 1.0307]
ED Visits	343.55	307.86	1.1160** [1.0762, 1.1572]
Outpatient Visits	725.47	530.70	1.3670** [1.3312, 1.4038]
	Completely Vaccinated	Partially Vaccinated	
Hospitalizations	46.65	51.44	0.9069* [0.8454, 0.9729]
ED Visits	346.19	343.55	1.0077 [0.9810, 1.0350]
Outpatient Visits	839.05	725.47	1.1566** [1.1358, 1.1777]
*p<.01, **p<.001			

Cases of nonspecific-diarrhea-coded illness, as well as mean and median cost of health care encounters by RV vaccine series completion are presented in Table 11. Highest mean cost among nonspecific-diarrhea-coded hospitalizations was found among unvaccinated children ($6,832.04), which is considerably larger than the mean for children who were partially ($4,856.25) or completely ($4,447.85) vaccinated against RV disease. There was no statistically significant difference in median costs for hospitalizations or emergency department visits by level of RV vaccine completion. A significant difference in median cost for nonspecific-diarrhea-coded coded outpatient visits between categories of RV vaccine series completion was noted (p<.0001). Partially vaccinated children had the highest median cost for outpatient visits ($85.39), and lowest median cost was found among children completely vaccinated against RV disease ($82.68). Although non-parametric analysis between groups was significant, the difference between highest and lowest mean cost of nonspecific-diarrhea-coded illness treated by outpatient providers was only $2.23.

Table 11

Cost of Nonspecific-Diarrhea-Coded Health Care Utilization

	RV Series Status	*N*	Mean	Median	IQR	*p*-value
Hospitalizations	Unvaccinated	869	6,832.04	2,559.83	337.96-5,784.08	0.8356
	Partially Vaccinated	1,082	4,856.25	2,550.86	1,028.13-4,903.75	
	Completely Vaccinated	2,773	4,447.85	2,505.57	1,142.34-4,734.01	
Emergency Department Visits	Unvaccinated	4,903	143.75	108.85	69.96-164.77	0.1826
	Partially Vaccinated	7,227	146.13	110.11	73.37-169.47	
	Completely Vaccinated	20,580	148.73	109.09	73.51-167.70	
Outpatient Visits	Unvaccinated	8,452	100.91	84.60	51.17-131.14	<.0001
	Partially Vaccinated	15,261	103.14	85.39	60.03-126.03	
	Completely Vaccinated	49,879	101.48	82.68	56.16-122.16	

Note. Mean, median, and interquartile range (IQR) values in $2017.

Discussion

Rotavirus vaccine coverage rates among Medicaid-insured children in Alabama lag behind national estimates. Among children aged 19 to 35 months living in poverty in Alabama, the National Immunization Survey (NIS) RV vaccine coverage estimate was 63.8% in 2011, 55.7% in 2012, 77.8% in 2013, 79.4% in 2014, 72.0% in 2015, and 61.5% in 2016 (Centers for Disease Control and Prevention, 2017a). The present study found coverage among Medicaid-insured infants in Alabama between 2010-2017 to be 56.31%. Although the CDC-reported NIS coverage estimates rely on dose count without consideration of ACIP-recommended age limits for RV vaccination, 2011-2016 estimates for RV coverage for Alabama children aged 19-35 months do not differ from those reported for seven month old infants (Centers for Disease Control and Prevention, 2017a). Despite differences in measurement between the NIS and the present study, it is important to note that the proportion of children in our study population that completed the RV vaccine series is considerably lower than the NIS-produced coverage estimate, which was limited to children living in poverty, for five out of six years between 2011 and 2016.

Although the proportion of children unvaccinated against RV in the present study is lower than that found in similar studies of Medicaid-insured children, the proportion of children who are completely vaccinated against RV disease falls well below the *Healthy People 2020* target of 80% (Calnan et al., 2016; Krishnarajah et al., 2015; United States Department of Health and Human Services, 2000). Furthermore, when compared to commercially-insured children, Medicaid-insured children are less likely to be vaccinated and are also less likely to be compliant with ACIP-recommendations with each successive dose in the RV vaccine series (Calnan et al., 2016; Panozzo et al., 2013).

Although RV vaccine effectiveness improves with each dose, both the full and partial series have been shown to be effective in providing protection against rotavirus illness requiring hospitalization or emergency department visits (Buttery et al., 2011; Curns et al., 2010; Dennehy et al., 2011; Desai et al., 2010; Donauer et al., 2013; Panozzo et al., 2014; Payne et al., 2015). When compared to children who had completed the full RV vaccine series, results of the present study demonstrated significantly higher incidence of RV illness that required hospitalization or an emergency department visit among unvaccinated and partially vaccinated children. Moreover, a higher incidence of RV-coded hospitalizations among unvaccinated children when compared to those who had completed a partial RV series. Overall, these results are similar to those found by other recent studies of RV vaccination. Krishnarajah et al. (2016) found that, among Medicaid-enrolled children, incidence of RV infection in unvaccinated children was twice that of completely vaccinated children. Within a population of commercially-insured children, a similar study found that compared to unvaccinated children, completely vaccinated children had lower rates of RV-associated hospitalizations, ER visits, and physician visits (Krishnarajah et al., 2017). In the present study, the mean cost of RV-coded health care utilization was higher among vaccinated children, which is contrary to results from other studies that showed unvaccinated children had higher mean costs than partially or completely vaccinated children in both Medicaid and commercially-insured populations (Krishnarajah et al., 2016; Krishnarajah et al., 2017).

Finally, incidence rates of Non-RV-coded hospitalizations of children who had completed the full RV vaccine series were significantly lower than for partially vaccinated or unvaccinated children. However, incidence of nonspecific-diarrhea-coded illness emergency department and outpatient visits among unvaccinated children were significantly lower than the rates for both partially or completely vaccinated children. Higher incidence of nonspecific-

diarrhea-coded illness in vaccinated children was not unexpected. Among Medicaid-enrolled children, Krishnarajah et al. (2016) found significantly higher incidence of diarrhea-coded inpatient visits, outpatient visits, and ER visits among both completely and incompletely vaccinated children when compared to unvaccinated children. Conversely, a recent study of commercially insured children found that, when compared to unvaccinated children, completely vaccinated children had significantly lower rates of diarrhea-coded inpatient and ER visits (Krishnarajah et al., 2017).

There are limitations to the current study. Age at time of illness was not assessed. The analysis of cases of illness may have included infants younger than 8 months old, meaning that health care utilization occurred before the determination of insurance status was made. The determination of RV vaccine series status was made using CPT codes in a Medicaid-claims database, which was designed for reimbursement for medical services rather than for the purposes of research. Furthermore, health care provider category was defined by an existing place of service categorization included in the Medicaid database, and the possibility of misclassification could not be eliminated. Finally, mean person-months of observation for unvaccinated children in the study population was lower than that for vaccinated children, which could have an impact on number of cases of illness and health care utilization costs.

Conclusions

The present study found incidence of severe cases of RV-coded and nonspecific-diarrhea-coded illness that required hospitalization was lowest among completely vaccinated children. Initiation of the RV vaccine series also provided protection against severe RV-coded illness as partially vaccinated children also had significantly lower incidence of RV-coded hospitalizations when compared to unvaccinated children. Among RV-coded cases treated in emergency

departments, completely vaccinated children had significantly lower rates of illness when compared to partially vaccinated and unvaccinated children. In addition, we found no significant differences in health care utilization of outpatient facilities for less severe cases of RV-coded illness by RV vaccine status. Although no differences were found in median costs for RV-coded health care utilization, our results support conclusions from studies of RV vaccine effectiveness. Receipt of any dose of RV vaccine provides protection against severe RV-coded illness; however, completion of the RV vaccine series maximizes protection against severe cases of RV-coded and diarrhea-coded illness.

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Appendix
International Classification of Diseases Codes

Rotavirus and Nonspecific Diarrhea ICD Codes

ICD-9	ICD-9 Description	ICD-10	ICD-10 Description
008.61	Enteritis due to rotavirus	A08.0	Rotavirual enteritis
558.9	Presumed noninfectious gastroenteritis	K52.89	Other specified noninfective gastroenteritis and colitis
787.91	Diarrhea	K52.2	Allergic and dietetic gastroenteritis and colitis
787.91	Diarrhea	R19.7	Diarrhea, unspecified
787.91	Diarrhea	K52.89	Other specified noninfective gastroenteritis and colitis
008.62	Enteritis due to adenovirus	A08.2	Adenoviral enteritis
008.63	Enteritis due to norwalk virus	A08.11	Acute gastroenteropathy due to Norwalk agent
008.64	Enteritis due to other small round viruses [SRV's]	A08.19	Acute gastroenteropathy due to other small round viruses
008.65	Enteritis due to calicivirus	A08.31	Calicivirus enteritis
008.66	Enteritis due to astrovirus	A08.32	Astrovirus enteritis
008.67	Enteritis due to enterovirus nec	A08.39	Other viral enteritis
008.69	Enteritis due to other viral enteritis	A08.39	Other viral enteritis
008.8	Intestinal infection due to other organism, not elsewhere classified	A08.8	Interstinal infection due to other organism not elsewhere classified
001.0	Cholera due to vibrio cholerae	A00.0	Cholera due to Vibrio cholerae 01, biovar cholerae
001.1	Cholera due to vibrio cholerae el tor	A00.1	Cholera due to Vibrio cholerae 01, biovar eltor
001.9	Cholera, unspecified	A00.9	Cholera, unspecified
002.0	Typhoid fever	A01.00	Typhoid fever, unspecified
002.1	Paratyphoid fever A	A01.1	Paratyphoid fever A
002.2	Paratyphoid fever B	A01.2	Paratyphoid fever B
002.3	Paratyphoid fever C	A01.3	Paratyphoid fever C
002.9	Paratyphoid fever, unspecified	A01.4	Paratyphoid fever, unspecified
003.0	Salmonella gastroenteritis	A02.0	Salmonella enteritis
003.1	Salmonella septicemia	A02.1	Salmonella sepsis
003.21	Salmonella meningitis	A02.21	Salmonella meningitis
003.22	Salmonella pneumonia	A02.22	Salmonella pneumonia

003.23	Salmonella arthritis	A02.23	Salmonella arthritis
003.24	Salmonella osteomyelitis	A02.24	Salmonella osteomyelitis
003.29	Other localized salmonella infections	A02.29	Salmonella with other localized infection
003.8	Other specified salmonella infections	A02.8	Other salmonella infections
003.9	Salmonella infection, unspecified	A02.9	Salmonella infection, unspecified
004.0	Shigella dysenteriae	A03.0	Shigellosis due to Shigella dysenteriae
004.1	Shigella flexneri	A03.1	Shigellosis due to Shigella flexneri
004.2	Shigella boydii	A03.2	Shigellosis due to Shigella boydii
004.3	Shigella sonnei	A03.3	Shigellosis due to Shigella sonnei
004.8	Other specified shigella infections	A03.8	Other shigellosis
004.9	Shigellosis, unspecified	A03.9	Shigellosis, unspecified
005.0	Staphylococcal food poisoning	A05.0	Foodborne staphylococcal intoxication
005.1	Botulism food poisoning	A05.1	Botulism food poisoning
005.2	Food poisoning due to Clostridium perfringens (C. welchii)	A05.2	Foodborne Clostridium perfringens [Clostridium welchii] intoxication
005.3	Food poisoning due to other Clostridia	A05.8	Other specified bacterial foodborne intoxications
005.4	Food poisoning due to Vibrio parahaemolyticus	A05.3	Foodborne Vibrio parahaemolyticus intoxication
005.81	Food poisoning due to Vibrio vulnificus	A05.5	Foodborne Vibrio vulnificus intoxication
005.89	Other bacterial food poisoning	A05.4	Foodborne Bacillus cereus intoxication
005.89	Other bacterial food poisoning	A05.8	Other specified bacterial foodborne intoxications
005.9	Food poisoning, unspecified	A05.9	Bacterial foodboorne intoxication, unspecified
008.00	Intestinal infection due to E. coli, unspecified	A04.4	Other intestinal Escherichia coli infections
008.01	Intestinal infection due to enteropathogenic E. coli	A04.0	Enteropathogenic Escherichia coli infection
008.02	Intestinal infection due to enterotoxigenic E. coli	A04.1	Enterotoxigenic Escherichia coli infection
008.03	Intestinal infection due to enteroinvasive E. coli	A04.2	Enteroinvasive Escherichia coli infection
008.04	Intestinal infection due to enterohemorrhagic E. coli	A04.3	Enterohemorrhagic Escherichia coli infection
008.09	Intestinal infection due to other intestinal E. coli infections	A04.4	Other intestinal Escherichia coli infections
008.1	Intestinal infection due to arizona group of paracolon bacilli	A04.8	Other specified bacterial intestinal infections
008.2	Intestinal infection due to aerobacter aerogenes	A04.8	Other specified bacterial intestinal infections
008.3	Intestinal infection due to proteus (mirabilis) (morganii)	A04.8	Other specified bacterial intestinal infections

008.41	Intestinal infection due to staphylococcus	A04.8	Other specified bacterial intestinal infections
008.42	Intestinal infection due to pseudomonas	A04.8	Other specified bacterial intestinal infections
008.43	Intestinal infection due to campylobacter	A04.5	Campylobacter enteritis
008.44	Intestinal infection due to yersinia enterocolitica	A04.6	Enteritis due to Yersinia enterocolitica
008.45	Intestinal infection due to Clostridium difficile	A04.7	Enterocolitis due to Clostridium difficile
008.46	Intestinal infection due to other anaerobes	A04.8	Other specified bacterial intestinal infections
008.47	Intestinal infection due to other gram-negative bacteria	A04.8	Other specified bacterial intestinal infections
008.49	Intestinal infection due to other organisms	A04.8	Other specified bacterial intestinal infections
008.5	Bacterial enteritis, unspecified	A04.9	Bacterial intestinal infection, unspecified
006.0	Acute amebic dysentery without mention of abscess	A06.0	Amebiasis
006.1	Chronic intestinal amebiasis without mention of abscess	A06.1	Chronic intestinal amebiasis
006.2	Amebic nondysenteric colitis	A06.2	Amebic nondysenteric colitis
006.8	Amebic infection of other sites	A06.89	Other amebic infections
006.9	Amebiasis, unspecified	A06.9	Amebiasis, unspecified
007.0	Balantidiasis	A07.0	Other protozonal intestinal diseases
007.1	Giardiasis	A07.1	Giardiasis [lambliasis]
007.2	Coccidiosis	A07.3	Isosporiasis
007.3	Intestinal trichomoniasis	A07.8	Other specified protozoal intestinal diseases
007.4	Cryptosporidiosis	A07.2	Cryptosporidiosis
007.5	Cyclosporiasis	A07.4	Cyclosporiasis
007.8	Other specified protozoal intestinal diseases	A07.8	Other specified protozoal intestinal diseases
007.9	Unspecified protozoal intestinal disease	A07.9	Protozoal intestinal disease, unspecified
0090	Infectious colitis, enteritis, and gastroenteritis	A09	Infectious gastroenteritis and colitis, unspecified
0091	Colitis, enteritis, and gastroenteritis of presumed infectious origin	A09	Infectious gastroenteritis and colitis, unspecified
0092	Infectious diarrhea	A09	Infectious gastroenteritis and colitis, unspecified
0093	Diarrhea of presumed infectious origin	A09	Infectious gastroenteritis and colitis, unspecified

Note. (Centers for Medicare and Medicaid Services, 2014, 2015, 2018)

CONCLUSION

Overall, there is a disproportionate rotavirus disease burden among Medicaid-insured children (Ma et al., 2009). Since implementation of routine rotavirus vaccination, children enrolled in Medicaid have had less disease reduction, as well as higher costs of rotavirus-associated health care (Krishnarajah et al., 2016). Racial, geographic, and socio-economic disparities, as well as disparities by insurance type in RV vaccine coverage, are noted in the literature (Centers for Disease Control and Prevention, 2017a; Hill, 2016; Hill et al., 2015; Krishnarajah et al., 2016). The complete RV vaccine series is highly effective, with effectiveness improving with each dose in the series (Boom et al., 2010; Donauer et al., 2013; Payne et al., 2013; Payne et al., 2015; Staat et al., 2011). Rotavirus vaccine coverage is consistently lower among impoverished children and children who reside in rural areas. Because low income and rural children are less likely to complete the series, evaluation of differences between infants who initiate and those who complete the full RV vaccine series is important.

The evaluation of health care utilization by RV series completion found that incidence of RV illness that required hospitalization or care in the emergency department was significantly lower among children who had completed the full RV vaccine series when compared to both partially vaccinated and unvaccinated children. Moreover, partially vaccinated children had significantly fewer RV-associated hospitalizations as compared to unvaccinated children. However, there were no significant differences in median costs of RV-associated health care utilization between the levels of series completion.

Almost 77% of Medicaid-insured infants in Alabama received at least one dose of RV vaccine between 2010-2017. However, only 56.3% of infants completed the full RV vaccine series. Significant differences in series completion were found by race, rural residence, provider specialty, and type of provider practice. Furthermore, receipt of all age-appropriate DTaP doses (≥3), and receipt of the RV1 vaccine type were the strongest predictors of RV vaccine series completion in the study population. Minimizing missed opportunities for simultaneous administration of childhood vaccinations could lead to improvements in RV vaccine coverage in this population. Almost 63% of the study population had completed all age-appropriate doses of the DTaP series, which are recommended at the same age ranges as doses of the RV vaccine. Further improvements in coverage could be achieved through examination of RV vaccine type. Almost 85% of infants administered doses of RV1 completed the series compared to just 71% of infants who received RV5 doses. Although the results of this study and others indicate increased likelihood for completion with receipt of RV1, more than 75% of infants who initiated the series received the RV5 vaccine.

Overall, a substantial proportion of Medicaid-enrolled infants in Alabama initiated the RV vaccine series. However, the proportion of infants who completed the series by the ACIP-recommended upper age limit was considerably lower than current coverage estimates for the state and the *Healthy People 2020* target of 80% (United States Department of Health and Human Services, 2000).In an effort to mitigate the impact of strict age limits for administration of RV vaccine doses, encouragement of RV vaccination among the unvaccinated should begin early in infancy. Furthermore, through substitution of vaccine type and maximization of simultaneous administration for all age appropriate vaccinations, improvement in vaccine series completion among infants who initiate the RV vaccine series may be possible.

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APPENDIX: INSTITUTIONAL REVIEW BOARD APPROVAL LETTER

THE UNIVERSITY OF ALABAMA | Office of the Vice President for Research & Economic Development
Office for Research Compliance

March 23, 2018

Randi Henderson
Rural Health
CCHS
Box 870326

Re: IRB#: 18-OR-121-ME "Impact of Rotavirus Vaccine Series Initiation and Completion"

Dear Randi Henderson:

The University of Alabama Institutional Review Board has granted approval for your proposed research.

Your application has been given expedited approval according to 45 CFR part 46. You have also been granted the requested waiver of informed consent. Approval has been given under expedited review category 5 as outlined below:

(5) Research involving materials (data, documents, records or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis)

Your application will expire on March 22, 2019. If your research will continue beyond this date, complete the relevant portions of the IRB Renewal Application. If you wish to modify the application, complete the Modification of an Approved Protocol Form. Changes in this study cannot be initiated without IRB approval, except when necessary to eliminate apparent immediate hazards to participants. When the study closes, complete the appropriate portions of the IRB Request for Study Closure Form.

Should you need to submit any further correspondence regarding this proposal, please include the above application number.

Good luck with your research.

Sincerely,

Carpantato T. Myles, MSM, CIM, CIP
Director & Research Compliance Officer

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