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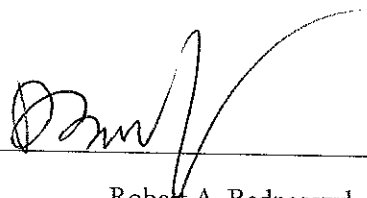
Missed Opportunities for Rotavirus Vaccination among U.S. Children 19-35 Months of Age

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Abstract

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By Bethany K. Sederdahl

Introduction: Rotavirus remains a common cause of severe gastroenteritis, resulting in hospitalization of about 5 per 10,000 children in the U.S. each year. Available rotavirus vaccines, although effective, are underused compared with other routine childhood vaccines. Receipt of other routine childhood immunizations, such as DTaP or PCV, at 2 and 4 months of age among children unvaccinated for rotavirus indicates a missed opportunity to simultaneously vaccinate for rotavirus. In this study, we analyzed missed opportunities for rotavirus vaccination in children included in the 2014 National Immunization Survey.

Methods: All analyses were conducted using data from the 2014 National Immunization Survey (NIS) available from the Centers for Disease Control and Prevention (CDC). We classified missed opportunities for rotavirus vaccination according to the ACIP and WHO rotavirus vaccine recommendations. Doses of DTaP vaccine received from 6 weeks through 7 months and 6 days of age were considered missed opportunities for rotavirus vaccine according to ACIP guidelines. Doses of DTaP or MMR received from 6 weeks to 24 months of age were considered missed opportunities for any dose of rotavirus vaccine according to the World Health Organization recommendation.

Results: Seventy-one percent of children in the 2014 NIS were vaccinated for rotavirus. Among the 14% of children unvaccinated for rotavirus, 72% had ≥ 1 ACIP-defined missed opportunity to receive rotavirus vaccine and 63% had ≥ 2 missed opportunities. Among children unvaccinated for rotavirus, 83% had ≥ 1 WHO-defined missed opportunity to receive rotavirus vaccine and 75% had ≥ 2 missed opportunities. We found that complete rotavirus vaccine coverage may be improved from 71% to 81% if all missed opportunities within the ACIP-recommended schedule were used. Additionally, we found that 97% complete coverage would be achievable if rotavirus vaccine were given simultaneously with DTaP or MMR through 24 months of age.

Conclusion: Addressing missed opportunities for rotavirus vaccination may be an important step towards achieving 80% rotavirus vaccine coverage, the target outlined by Healthy People 2020. Although expanding the window for rotavirus vaccination through 24 months of age may provide an opportunity to increase coverage, safety concerns may prohibit use of this option in the U.S.

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CHAPTER I: Literature Review

Overview

Rotavirus was linked with gastroenteritis in 1973 when the virus was visualized in small intestine epithelial tissue from children hospitalized with acute diarrhea in Australia. (1) Since its discovery, rotavirus has been recognized as a leading cause of acute gastroenteritis and diarrhea-attributable deaths. (2) Globally, an estimated 500,000 childhood deaths were attributed to rotavirus in the year 2000. The greatest burden of rotavirus mortality lies in Sub-Saharan Africa and Southeast Asia. It is estimated that 90% of rotavirus-associated mortality occurs in low-resource countries in these regions. (3) Overall, 9% of under 5 child mortality is attributed to diarrhea, and ~40% of these deaths are attributed to rotavirus. (3, 4) Although most rotavirus-associated mortality occurs in low-income countries, rotavirus has also caused a substantial burden of disease in the U.S. In the U.S., 410,000 pediatric healthcare encounters, 50-70,000 hospitalizations, and ~40% of outpatient visits for acute gastroenteritis were attributed to rotavirus annually prior to the availability of rotavirus vaccines. (5) In 2006 and 2008, two rotavirus vaccines were licensed, and their use has dramatically impacted the burden of rotavirus disease where vaccines are available. In the U.S., rotavirus vaccines reduced rotavirus-coded hospitalizations by 60-94% (varies by year). (6) However, rotavirus continues to cause gastroenteritis-related hospitalizations in an estimated 5 per 10,000 children annually in the U.S. (7) Globally, rotavirus was estimated to cause ~200,000 under 5 child deaths in 2013. (4) Rotavirus continues to be an important cause of disease worldwide.

Rotavirus natural history

Rotaviruses belong to the *Reoviridae* family of viruses and are comprised of 8 species, or groups. Group A rotaviruses are most common and, with few exceptions, are the major cause of rotavirus disease in humans. (8) Rotavirus, referred to as a triple-layered particle (TLP), has three concentric protein shells that surround the virus's genome. Rotavirus has an 11-segment double-stranded RNA genome that codes 12 proteins, 6 structural (VP1-6) and 6 nonstructural (NSP1-6). (9) Structural proteins VP4 and VP7 are important neutralizing antigens that determine the serotype of the virus. VP4 is a spoke-like attachment protein in the outer layer of the virus that gives it its characteristic appearance. (10) VP4 corresponds with P typing. VP7, also in the outer layer, is a glycoprotein that corresponds with G typing (11) At least 27 different G-proteins and 37 P-proteins have been identified in Group A rotaviruses. (9) Early in rotavirus vaccine development, it was discovered that VP4 and VP7 independently have the ability to evoke

antibodies that can neutralize virus infectivity and these proteins have played an important role in rotavirus vaccine development. (12)

Before rotavirus vaccine introduction, five strains of rotavirus (G1-4, G9) accounted for an estimated 88% of isolates from children globally. Of these, the G1 strain accounted for more than 40% of isolates, most of which were G1P8. (13) Strain distribution in the U.S. reflected that seen globally, but was less diverse. More than 90% of typed rotavirus strains were G1, G2, or G9, with G1P8 alone accounting for nearly 80% of typed isolates. (14) Surveillance of rotavirus genotypes has remained a public health priority since vaccine introduction in order to monitor for possible vaccine selection pressure that could alter the distribution of disease-associated strains. Since vaccine introduction in the U.S., rotavirus strains G3P8 then G12P8 have become the predominant strains. It has been determined that this change is likely attributable to natural drift, rather than vaccine-induced selection pressure. (15) Globally, the distribution of genotypes from 2007-2012 has been found to be similar to that seen before vaccine introduction. (8, 16) Currently, there is no evidence of vaccine use inducing selection pressure on rotavirus strains; however, surveillance remains a priority to continue to monitor strains of rotavirus associated with human disease.

Rotavirus epidemiology and disease process

In temperate climates, rotavirus appears in winter-spring seasonal peaks causing gastroenteritis. An increase in rotavirus infections is typically first seen in the Southwestern U.S. in December, then infection is seen until March or April of the following year. (17) In the 1990s, it was estimated that rotavirus accounted for 25-50% of gastroenteritis cases resulting in hospitalization in children in the U.S. (18) Nearly all children have an initial infection with rotavirus by 2 years of age and most will be infected more than once. Subsequent infections are usually less severe, but can still result in symptomatic illness. (19) In a study conducted in Mexico, it was found that the initial rotavirus infection provides 87% protection against moderate to severe second infection, while a second infection achieves 100% protection against a third infection. Rotavirus is spread by fecal-oral transmission, and is highly infectious. One gram of stool from an infected individual has been estimated to contain 10^{10} virions, while an infectious dose may be as small as 10 particles. (20) Additionally, the virus is very stable and may remain viable in the environment for weeks or months if surfaces are not disinfected. The incubation period after exposure to the virus is about 48 hours. (20) Rotavirus causes acute gastroenteritis frequently characterized by fever, vomiting, and most notably profuse, non-bloody diarrhea. (21) Infected children typically experience 10-20 episodes of diarrhea per day, and as a result can quickly develop severe dehydration. (10) Rotavirus infections occur most frequently in children 6 months to 2 years of age. (21) Risk factors for rotavirus hospitalization in the U.S. include presence of another child less than 2 years of

age in the household, non-receipt of breastmilk, daycare attendance, and socioeconomic factors including young maternal age and uninsured status. (22)

While there are no antiviral medications for the treatment of rotavirus gastroenteritis, recommendations for children hospitalized with severe dehydration include oral rehydration therapy or intravenous fluid replacement. (23) Antidiarrheal, antiemetic, or antipyretic medication may also be given to relieve symptoms, which without intervention typically resolve in 3-7 days. (24)

Host genetic susceptibility plays an important role in rotavirus infection and severity of symptoms. (25) Rotaviruses bind to histo-blood group antigens, which are oligosaccharides found in epithelial cells of the gastrointestinal and respiratory tracts. Individuals who express these antigens in gastrointestinal epithelial cells are more likely to develop rotavirus disease. (25, 26) The expression of histo-blood group antigens is determined by activity of the FUT2 gene. Those with functioning FUT2 gene express antigen and are referred to as secretors, while those without an active FUT2 gene are referred to as non-secretors. In European-descendent populations, non-secretors comprise about 20% of individuals. (25) Secretors are at higher risk for severe rotavirus disease than non-secretors.

The mechanism by which rotavirus causes diarrhea remains unclear. It has been attributed to malabsorption resulting from damaged enterocytes, a nervous system response triggered by damaged enterocytes, villous ischemia, and NSP4 enterotoxin activity. (27, 28) Villous enterocytes, the target cells for rotavirus attachment, are non-proliferative cells differentiated to synthesize enzymes important for digestion of carbohydrates and proteins. (28) Rotaviruses invade villous enterocytes by endocytosis through a Ca^{2+} -regulated mechanism, replicate, and alter the function of these cells in the small intestine. Enterocyte damage results in malabsorption that is partially responsible for rotavirus diarrhea. Death of enterocytes, or villous ischemia, follows infection. Ischemia of absorptive cells within the small intestine further contributes to malabsorption. In addition to malabsorption, rotavirus infection has also been associated with stimulation of the enteric nervous system (ENS) resulting in increased gastric motility. Inhibiting activity of the ENS has been shown to notably reduce diarrhea in mice. (28) Additionally, studies in mice point towards NSP4, or certain NSP4 peptides, as an enterotoxin capable of inducing diarrhea. (27) In summary, mechanisms of rotavirus diarrhea are complex and not explained by a single process. Combined evidence suggests that both host and viral factors affect severity of disease.

History of rotavirus vaccines in the U.S.

Initial bovine and rhesus rotavirus vaccines were developed in the 1980s, but neither were effective in preventing severe rotavirus disease. In 1998, RotaShield was the first rotavirus vaccine licensed. (29) RotaShield was a tetravalent rotavirus vaccine (RRV-TV) developed from a rhesus rotavirus reassorted

with three human rotavirus VP7 proteins, corresponding to G-types 1, 2, and 4. (30) During pre-licensure trials in the United States, Finland, and Venezuela, RotaShield proved highly effective in the prevention of severe rotavirus gastroenteritis. (31, 32) During safety evaluations, it was noted that five cases of intussusception (telescoping of the intestine, potentially fatal if untreated) were seen among vaccinated children, whereas only one case was seen among the controls during pre-licensure trials. The rate of intussusception seen among the vaccinated children was consistent with the baseline rate of intussusception in the U.S., allaying concerns about vaccine safety. (33) However, less than a year after vaccine introduction and immunization of more than 600,000 infants, RotaShield was withdrawn in the U.S. due to safety concerns. (32) The actual risk of intussusception associated with rotavirus vaccination was difficult to assess since intussusception is a very rare outcome. However, it was determined that there was an increased risk of intussusception 3 to 10 days after receipt of oral vaccine. (29, 32) Early estimates warned of intussusception occurring in 1 of 2,500 vaccinated children, but ultimately RotaShield was estimated to cause intussusception in 1 of 10,000 vaccine recipients. (34)

Rejection of RotaShield in the U.S. had widespread global repercussions. The vaccine was no longer considered for use, even in regions of the world where the benefits of vaccination may have substantially outweighed the risk of intussusception. (33) The withdrawal of RotaShield underscores the fact that people are generally more accepting of “natural” harm than harm attributed to human intervention. (35) It may also be of note that RotaShield introduction in the U.S. coincided with publication of Wakefield’s controversial study correlating measles, mumps, rubella (MMR) vaccination and autism in *Lancet*. Skepticism surrounding the safety of routine vaccination after publication of Wakefield’s study was possibly a factor in poisoning public reception of a vaccine that posed any risk of adverse outcome. (33)

After withdrawal of RotaShield, rotavirus vaccine development remained a priority. In 2006, Merck obtained a license for RotaTeq (RV5) nearly eight years after RotaShield was withdrawn. RotaTeq is a live-attenuated, pentavalent vaccine created from a bovine rotavirus strain reassorted with human VP7 proteins corresponding to G-types 1, 2, 3, and 4 and human VP4 protein corresponding to P-type 8. (29) Before approval of RV5, a large pre-licensure trial assessing vaccine safety was conducted, enrolling more than 60,000 infants. RV5 was determined to be both effective and safe, with intussusception occurring in vaccinated and placebo groups with comparable frequency. (36) Passive vaccine safety reporting in the U.S. has provided information about the safety of RV5 post-licensure. Clustering of intussusception events has been identified within 3-6 days of the first dose of RV5. (37) Additionally, receipt of the first dose of RV5 has been associated with approximately 1.5 excess cases of intussusception per 100,000 recipients. (38) Regardless of the risk of intussusception associated with

RV5, the benefits of routine rotavirus vaccination in the U.S. have been determined to far outweigh small increased risk of intussusception. (39, 40)

Nearly two years after the introduction of RV5, Glaxo Smith Kline obtained a license for RotaRix (RV1) in the U.S. RotaRix is a live-attenuated, monovalent vaccine developed from human rotavirus antigens VP4 and VP7 corresponding to the G1P8 strain of virus, the most common circulating strain. (32) Large-scale, pre-licensure trials involving more than 60,000 infants conducted in Latin America and Finland established safety and efficacy of RV1. (41) Passive vaccine safety reporting in the U.S. has identified a clustering of intussusception events within 3-8 days of vaccination with the initial dose of RV1. (42) Estimates of excess intussusception risk with receipt of RV1 range from 1.2 -2.8 cases per 100,000 vaccine recipients. (42) However, the benefits of vaccination with RV1 outweigh the risk of intussusception. (39, 40) Trends in the rate of intussusception since introduction of RV5 and RV1 rotavirus vaccines have demonstrated no overall increased risk of intussusception. (43) However, the intussusception hospitalization rates for children 8-11 weeks of age were significantly elevated when compared with pre-vaccine baseline rates for intussusception. Since the first dose of rotavirus vaccine is often given from 8-11 weeks of age, the increased risk of intussusception may be attributable to rotavirus vaccination. However, the dramatic decline in rotavirus gastroenteritis hospitalizations and healthcare encounters since vaccine introduction compared to the small increased risk of intussusception provides strong support for the use of vaccines. (43)

Based on pre- and post-licensure evidence for the safety and efficacy of rotavirus vaccines, the Advisory Committee on Immunization Practices (ACIP) has established recommendations for the use of rotavirus vaccine. RV5 is an oral, live-attenuated vaccine administered in a three-dose series at 2, 4, and 6 months of age. RV1 is a two-dose series administered at 2 and 4 months of age. (44) If vaccine product is unknown for a dose of vaccine, a total of three doses of vaccine should be given. The ACIP has recommended initiation of rotavirus vaccine (either product) only between 6 weeks of age and 14 weeks and 6 days of age. (44) The maximum age for receipt of any dose of rotavirus vaccine is 8 months and 0 days. (44)

Impact of rotavirus vaccines

Both licensed rotavirus vaccines have proven very effective in the prevention of rotavirus-associated healthcare encounters in the U.S. During pre-licensure clinical trials, complete RV5 vaccination was found to be 88-100% effective in the prevention of severe gastroenteritis. (36) Similarly, complete RV1 vaccination was found to be 85-100% effective in the prevention of severe gastroenteritis. (41) Post-licensure studies in the U.S. have provided estimates of rotavirus vaccine effectiveness, including

effectiveness against hospitalization, ED encounters, severe gastroenteritis, any symptomatic rotavirus infection, or effectiveness of partial vaccination against any of these outcomes. Rotavirus vaccine effectiveness is highest against severe gastroenteritis or hospitalization. (45) Effectiveness of complete RV5 vaccination against rotavirus-associated hospitalization or ED encounters ranges from 84-100%. (45, 46) Partial vaccination with RV5 is also effective in preventing hospitalization and ED visits. A single dose of RV5 has been found to be 88% effective in prevention of hospitalization and ED visits, and two doses are 94% effective. (47) Effectiveness of complete RV1 vaccination against hospitalization or ED encounters ranges from 70- 91%. (45, 46) Mixed dose (3 doses of either product) rotavirus vaccine effectiveness is comparable to that achieved with either complete series. (48, 49) Cross-strain protection, particularly of concern for RV1, has been demonstrated. (50, 51)

Rotavirus vaccines have dramatically decreased the burden of rotavirus-associated gastroenteritis hospitalizations, as well as all-cause acute gastroenteritis hospitalizations in the U.S. (52) The postvaccine (2008-2012) mean rotavirus-associated hospitalization rate of 16 per 10,000 children <5 years of age represents a 62-94% reduction from prevaccine (2000-2006) estimates. (52) The mean rate of all-cause gastroenteritis hospitalization postvaccine is 76 per 10,000 children <5 years of age, a 31-55% reduction from prevaccine estimates. (52) The National Respiratory and Enteric Virus Surveillance System (NREVSS), a national laboratory reporting system, has reported declines in rotavirus detection ranging from 58-90% since vaccine introduction. (53) While 26% of rotavirus tests performed from 2000-2006 were positive, the proportion positive from 2007-2014 varied from 4 to 11%. (53) The range in rotavirus detection rates postvaccine is partly explained by the bi-seasonal pattern of rotavirus disease that has emerged since rotavirus vaccine introduction discussed further below. (54) Shortly after rotavirus introduction, evidence of substantial indirect protection conferred to unvaccinated children and adults was evident.

Reductions in rotavirus-associated and all-cause gastroenteritis hospitalizations have been described not only in young children, but also in older children and adults. (55, 56) Significant decreases in rotavirus disease have been seen in unvaccinated individuals 5 to ≥ 65 years of age. (55) In an adult study conducted at an urban hospital in the Midwest, the prevalence of rotavirus in a convenience sample of diarrheal stool specimens was 4% in 2006-2007 compared to 2% in 2008-2010 (~50% reduction). (56) Indirect protection, also referred to as 'herd immunity,' has been an important factor in the success of rotavirus vaccines in the U.S.

The seasonal pattern of rotavirus disease has changed since the introduction of rotavirus vaccines. Before vaccine introduction, rotavirus disease peaked each year during the winter-spring months. Since vaccine introduction, rotavirus disease continues to peak each winter-spring but with much higher prevalence in

“odd” years. The National Respiratory and Enteric Virus Surveillance System (NREVSS) reported rotavirus detection rates of ~10% in during “odd” years postvaccine (2009, 2011, 2013, 2015). In contrast, ~4% rotavirus detection rates were reported in “even” years postvaccine (2008, 2010, 2012, 2014). (57) One commercial laboratory that performs a large volume of rotavirus tests annually reported ~6% positivity in rotavirus tests from children <10 years of age (2008-2014). (58) The proportion of positive tests ranged from 2-6% in even years and from 7-8% in odd years. (58) As expected, the bi-seasonal surges in rotavirus detection described are accompanied by an increase in rotavirus gastroenteritis-associated healthcare encounters in odd years. In an analysis of gastroenteritis-associated hospitalizations, the rate positive in even and odd years postvaccine was compared with the rate positive during prevaccine years. Compared with pre-vaccine rates (2001-2006), rotavirus-coded hospitalization rates among unvaccinated children decreased by 77% in 2009-2010 (even year) but only by 25% in 2010-2011 (odd year). (6) From 2008-2012, even years postvaccine had a 48-55% decrease in rotavirus hospitalization, while odd years postvaccine had a 33-47% rate of decrease compared to prevaccine hospitalization estimates. (52) In addition to developing a biennial pattern, rotavirus seasons have been described as shorter and later postvaccine. (54)

The changes seen in rotavirus seasonality since vaccine introduction are not fully understood. However, it is possible that low rotavirus vaccine coverage in the U.S. determined the changes in rotavirus seasonality. Rotavirus vaccine coverage rapidly increased to ~70% by 2010, but has not improved in recent years. (59) Since ~20% of vaccine-eligible children in the U.S. are unvaccinated against rotavirus, a sufficient population of rotavirus-susceptible children may accumulate every 2 years to amplify rotavirus transmission. (52, 60) The median age of rotavirus-infected children seeking healthcare has increased since vaccine introduction. (60) The increased age of rotavirus-positive children, particularly pronounced in odd seasons, may be explained by delayed age of infection in children temporarily shielded from rotavirus by indirect protection. (60) In countries with higher rotavirus vaccine coverage, biennial peaks of disease have not developed. (61, 62)

In summary, it is clear that rotavirus disease has dramatically declined since the introduction of vaccines. However, biennial peaks of rotavirus-associated gastroenteritis and resulting healthcare encounters among children in the U.S. continue. It is estimated that rotavirus continues to cause gastroenteritis-related hospitalizations in about 5 per 10,000 children in the U.S. (7) The residual burden of rotavirus disease in the U.S. may be impacted by increasing rotavirus vaccine coverage.

Use of rotavirus vaccines

After licensure, rotavirus vaccine coverage rapidly increased reaching 44% by 2009. (63) Use of rotavirus vaccine continued to increase, and by 2012 coverage was estimated at 69%. In the past several years, however, coverage has remained at ~70%. (59, 63) Reports from the National Immunization Survey indicate that only 73% of children 19-35 months of age were completely vaccinated for rotavirus in 2015. (59) Failure to vaccinate for rotavirus has been clearly linked with risk for rotavirus disease, and improving uptake of available rotavirus vaccines is a public health priority. (64) Healthy People 2020 states a target of 80% complete rotavirus vaccine coverage by year 2020. (65) In order to address barriers to rotavirus vaccine use, it is important to describe the circumstances resulting in failure to use the vaccine. Specifically, efforts have been made to describe failures to receive rotavirus vaccine simultaneously with other routine childhood immunizations from missed vaccination visits. (66, 67) Two other routine childhood vaccines, DTaP (diphtheria-tetanus-acellular pertussis) and PCV (pneumococcal conjugate vaccine), are also given at 2, 4, and 6 months of age. (67) Coverage for ≥ 3 doses of DTaP (diphtheria-tetanus-acellular pertussis) vaccine and PCV (pneumococcal conjugate vaccine) each exceed $>90\%$ among children 19-35 months of age. (59) Assessing the magnitude and timing of missed opportunities for rotavirus vaccination simultaneous with DTaP and PCV vaccination has become a topic of interest. (59, 66, 68) Receipt of DTaP vaccine is a strong predictor for rotavirus vaccination. (69) However, the gap in vaccine coverage between rotavirus and DTaP indicates that there may be missed opportunities to vaccinate for rotavirus simultaneously with DTaP.

In a study of rotavirus vaccine coverage among children 5 months of age, missed opportunities to vaccinate for rotavirus simultaneously with other routine childhood immunizations were assessed. Data used in the study were collected from six different study sites that collectively capture ~10% of the U.S. pediatric population. (68) The average difference in coverage between DTaP and rotavirus vaccine in this study was ~6-8%. The researchers concluded that approximately one third of the difference in coverage may be due to the age restriction for rotavirus vaccine initiation. According to ACIP guidelines, rotavirus vaccination must be initiated between 6 and 15 weeks of age. (44) The other two-thirds of the difference appeared to be a result of missed opportunities to simultaneously vaccinate for rotavirus with DTaP or PCV. (68)

One large study of rotavirus vaccine use among privately-insured infants assessed rotavirus vaccination status at "milestone" ages and missed opportunities to vaccinate for rotavirus at well-child visits. (66) According to ACIP (Advisory Committee on Immunization Practices) guidelines, rotavirus vaccine should not be given after 8 months of age. (44) DTaP is routinely given up to 6 years of age and PCV up to 5 years of age. This study assessed whether the discrepancy in coverage rates between rotavirus

vaccine and DTaP or PCV arises during the first 7 months of life, or whether it arises after 8 months of age, outside the recommended age for rotavirus vaccination. The researchers concluded that rotavirus vaccine coverage is somewhat lower than DTaP or PCV coverage at 6 months of age, but that the coverage difference sharply increases after 7 months of age when catch-up doses of DTaP or PCV, but not rotavirus vaccine, can be given. (66) The gap in coverage between rotavirus vaccine and DTaP or PCV develops after children are no longer age-eligible for rotavirus vaccine. Regardless, most children unvaccinated for rotavirus had at least 1 missed opportunity for rotavirus vaccination. Among infants unvaccinated for rotavirus, 75% had a well-child visit while age-eligible for rotavirus vaccine initiation and 45% had a well-child visit while age-eligible for rotavirus vaccine doses 2 or 3. (66)

Rotavirus vaccine hesitancy

Missed opportunities to vaccinate for rotavirus at well-child visits where other vaccines are given may be attributable to provider attitudes or beliefs about rotavirus vaccines. Shortly after the introduction of pentavalent rotavirus vaccine, assessments of rotavirus vaccine use indicated higher usage among pediatricians than family practitioners. At the time the study was conducted (2007), both pediatricians and family practitioners reported the following barriers to vaccine use: lack of coverage by insurance companies, costs of purchasing vaccine, and lack of adequate reimbursement. Concerns about safety or adding an additional vaccine to the routine immunization schedule were more common among family practitioners than pediatricians. (70)

A later study assessing factors associated with failure to vaccinate for rotavirus identified healthcare provider attitudes, as well as parental concerns as possible causes of under-use of rotavirus vaccine in the U.S. The two current licensed rotavirus vaccines were received with suspicion by some healthcare providers after the safety concerns associated with Rotashield. Contamination of both RV1 and RV5 with porcine circovirus in 2010 also raised concerns about rotavirus vaccine safety. The Food and Drug Administration briefly suspended use of RV1 in order to investigate contamination. (71, 72) Although concerns about vaccine safety have decreased over time, reluctance to endorse rotavirus vaccination persists, particularly among family practitioners. (72) Routine administration of rotavirus vaccines has been found to be more common among pediatricians than family practitioners. (69, 72) It is clear that provider attitudes play an important role in rotavirus vaccine use, and it is important that healthcare professionals achieve a unified voice in promoting rotavirus vaccination. Mixed messages from healthcare professionals perpetuate doubts regarding the safety of available vaccines. (73)

Concerns about vaccine safety influence parents' willingness to allow their children to receive all recommended vaccines. In a large online survey study conducted in 2009, 12% of parents who responded

had refused at least 1 recommended vaccine for their child. In this study, women were more likely to be concerned about serious adverse events or believe that some vaccines cause autism. Hispanic parents were more likely to be compliant with vaccine recommendations. (74)

In a study of National Immunization Survey data from 2009, the relationship between parents' beliefs about vaccines and their child's vaccine status at 24 months of age was evaluated. (75) In this study, only 44% of parents neither delayed nor refused rotavirus vaccine, whereas 85% neither delayed nor refused DTaP. Among parents who delayed or refused rotavirus vaccination, 37% only delayed, 36% only refused, and 40% both delayed and refused vaccines. Parents who delayed or refused vaccines were more likely to have vaccine safety concerns and doubt the benefits of vaccination. (75)

Children at risk for non-receipt of rotavirus vaccine

Several patient-level factors have also been associated with failure to vaccinate for rotavirus. Foreign birth is strongly associated with non-receipt of rotavirus vaccine. In a summary of National Immunization Survey data from 2010-2012, 66% of U.S.-born infants had received ≥ 1 dose of rotavirus vaccine, whereas 16% of foreign-born infants had received any rotavirus vaccine. (76) Additionally, National Immunization Survey analyses reveal lower rotavirus vaccine coverage among children who reside in a suburban or rural area versus an urban area. Socioeconomic disparities in vaccine coverage were also recognized. (69) Children considered to have low socioeconomic status were less likely to receive rotavirus vaccine.

Infants who have been admitted to the NICU are at risk for not receiving rotavirus vaccine, leaving these children susceptible to rotavirus disease. (64, 77) Vaccination of infants who remain in the NICU through the maximum age for rotavirus vaccination is not recommended since concern regarding live-attenuated vaccine strain transmission among hospitalized infants exists. Recent evidence suggests that the benefits of NICU vaccination would outweigh the potential risk of vaccine strain transmission; however, most NICU guidelines prohibit rotavirus vaccine administration in the NICU. (77, 78)

Risk factors for partial rather than complete vaccination are poorly described. However, it has been found that infants who receive pentavalent rotavirus vaccine (3-dose series) are less likely to finish the rotavirus vaccine series than those who are vaccinated with monovalent rotavirus vaccine (2-dose series). (69) In the U.S., most children (70-90%) vaccinated for rotavirus receive pentavalent vaccine (3-dose series). (79)

Considerations for global vaccine use

The World Health Organization (WHO) has universally recommended rotavirus vaccines since 2009. The high burden of rotavirus vaccine in Sub-Saharan Africa and Southeast Asia make these low-resource regions important targets for rotavirus vaccine use. Gavi, the Vaccine Alliance is a public-private global health partnership that has played an important role in addressing cost-barriers to rotavirus vaccine coverage in low-resource countries. Thirty-eight countries currently using rotavirus vaccines are Gavi-funded. (80) However, WHO reported in 2015 that rotavirus vaccine is used in 86 countries, including 23 in Africa but none in Southeast Asia. (81, 82) Cost continues to be a significant barrier to rotavirus vaccine introduction in many low and middle-income countries. Development of alternative rotavirus vaccines, such as Bharat Biotech's development of Rotavac, a lower-cost, monovalent rotavirus vaccine, may play an important role in further increasing rotavirus vaccine protection in low-resource settings. (83, 84) In 2014, Rotavac was licensed in India and vaccine effectiveness reports are not yet available. However, a surveillance system is in place to monitor the impact of rotavirus vaccine in India, the country known for having the highest burden of rotavirus disease. (83)

In low-resource settings where rotavirus vaccines have been introduced, vaccine effectiveness has been lower than that seen in higher-resource settings. (85) In a systematic review of rotavirus vaccine effectiveness analyses, vaccines were effective in preventing rotavirus diarrhea and hospitalizations across all regions. (86) However, efficacy against severe diarrhea was estimated at 91% in developed regions, but only ~50% in Latin America, Southern Asia, and sub-Saharan Africa. (86) Adjusting the timing or number of doses of rotavirus vaccine has been considered as a possible means of improving effectiveness of available vaccines in low-resource settings. (87)

In 2013, WHO recommended a more flexible rotavirus vaccination schedule that allows receipt of the first dose of rotavirus vaccine up to 24 months of age. Expanding the age for initiation was intended to encourage vaccination globally, particularly in regions where rotavirus vaccine initiation is not feasible between 6 and 15 weeks of age. (2, 88)

Conclusion

Rotavirus vaccines have dramatically decreased the occurrence of severe rotavirus diarrhea, both in the U.S. and globally. Increasing use of licensed rotavirus vaccines in the U.S. would likely further decrease the burden of disease, and perhaps diminish the bi-seasonal peaks of rotavirus disease that persist after vaccine introduction. Increased uptake of rotavirus vaccines in the U.S. may be possible by influencing clinician attitudes towards the use of rotavirus vaccination. Since most children who are unvaccinated for rotavirus had a missed opportunity to receive rotavirus vaccine simultaneously with other childhood

vaccinations, influencing provider attitudes towards rotavirus vaccination may be an important step towards closing the gap between rotavirus and DTaP/ PCV vaccine coverage.

Two studies have provided important information regarding missed opportunities for rotavirus vaccination in the U.S. The first assessed missed opportunities to vaccinate for rotavirus with DTaP in privately-insured children 2 years of age, and the other assessed missed opportunities to vaccinate for rotavirus among children 5 months of age. (66, 68) In our study, we analyzed National Immunization Survey data from 2014 in order to summarize the number of missed opportunities to vaccinate for rotavirus simultaneously with DTaP. We assessed missed opportunities from 6 to 15 weeks, 15 weeks to 8 months, and 6 weeks to 24 months of age. These ages represent missed opportunities for vaccine initiation, vaccine doses 2 or 3, and all vaccine doses within the WHO-recommended expanded schedule, respectively. (2, 89) We also considered characteristics associated with failure to initiate or complete the rotavirus vaccine series, such as family income, number of children in the household, and provider location. Our objective was to quantify missed opportunities to receive rotavirus vaccine simultaneously with other routine childhood immunizations, and to describe characteristics associated with failure to receive rotavirus vaccine among children 19-35 months of age included in the 2014 National Immunization Survey.

CHAPTER II: Manuscript

Introduction

Before rotavirus vaccine introduction, rotavirus disease caused an estimated 200,000 emergency outpatient visits and 50-70,000 hospitalizations each year among children <5 years of age in the U.S. (90) Twenty-five to fifty percent of gastroenteritis-associated hospitalizations in U.S. children were attributed to rotavirus. (18) Rotavirus vaccines, introduced in 2006 and 2008, dramatically impacted the burden of rotavirus disease in the U.S., reducing rotavirus-attributed hospitalizations by 70-80%. (90, 91) Despite this success, rotavirus disease remains a common cause of severe gastroenteritis, resulting in hospitalization of about 5 per 10,000 children in the U.S. each year. (3) Vaccine coverage reports from the National Immunization Survey for 19-35 month old children indicate that only 73% of vaccine-eligible children 19-35 months of age were completely vaccinated for rotavirus in 2015, whereas coverage for ≥ 3 doses of DTaP (diphtheria-tetanus-acellular pertussis) vaccine and PCV (pneumococcal conjugate vaccine) each exceeded 90%. (59) Failure to vaccinate for rotavirus has been clearly linked with risk for rotavirus disease, and improving uptake of available rotavirus vaccines is a public health priority. (64)

The Advisory Committee on Immunization Practices (ACIP) recommends giving the first dose of rotavirus vaccine by 6 weeks of age, but no later than 14 weeks and 6 days of age. Following doses should be given before 8 months and 0 days of age. (92) The age restrictions selected by the ACIP for rotavirus vaccine administration were informed by safety concerns. The first licensed rotavirus vaccine was withdrawn from use in 1999 after posing an increased risk of intussusception (telescoping of the bowel), and the safety of subsequent rotavirus vaccines has been carefully evaluated. The World Health Organization (WHO) has recommended administration of rotavirus vaccine up to 24 months of age. (93) Globally, particularly in low-resource settings, it is often impossible to initiate and complete vaccination before 8 months of age. In 2013, the WHO recommended initiating rotavirus vaccination up to 24 months of age, citing that potential benefits of vaccination would outweigh the small safety risks associated with vaccination of older children. In this study, we identified opportunities to improve rotavirus vaccine coverage in the U.S. by estimating missed opportunities for simultaneous DTaP and rotavirus vaccination within the ACIP-recommended rotavirus vaccination schedule. In order to evaluate the possible impact of expanding the rotavirus vaccination through 24 months of age, we also estimated missed opportunities to simultaneously vaccinate for rotavirus with DTaP or MMR through 24 months of age.

Methods

This study reviewed and not deemed human subjects research by the Emory University IRB. All analyses were conducted using data from the National Immunization Survey (NIS) available from the Centers for Disease Control and Prevention. (94) The NIS is a two-phase, nationally-representative telephone survey of parents of children 19-35 months of age in the U.S. Initially, parents are contacted by random digit dialing to obtain a child's vaccine history and demographic information. Following contact with parents, children's vaccine providers are contacted to verify vaccine information. Only provider-verified immunization data was included in this study.

Variable estimates and assumptions:

Completely vaccinated children were those who received 3 doses of RV5, 2 doses of RV1, or ≥ 3 doses of either vaccine type. Partially vaccinated children were those who received < 3 doses of RV5, 1 dose of RV1, or a combined series with < 3 doses. Unvaccinated children were those who received no doses of rotavirus vaccine. For sensitivity analysis (**Table 4**), complete rotavirus vaccination was conservatively considered 3 doses of rotavirus vaccine, since RV5 is the most frequently used rotavirus vaccine in the U.S.

DTaP or MMR vaccination was considered an opportunity to simultaneously vaccinate for rotavirus. We classified missed opportunities for rotavirus vaccination according to the ACIP and WHO rotavirus vaccine schedules. Doses of DTaP vaccine received from 6 weeks through 14 weeks and 6 days of age were considered missed opportunities for rotavirus vaccine initiation according to ACIP recommendations. Those received from 15 weeks through 7 months and 6 days of age were considered missed opportunities for rotavirus vaccine doses 2 or 3. They were not considered missed opportunities for rotavirus dose 1 since children in this age group were beyond the maximum age for dose 1. Doses of DTaP or MMR received from 6 weeks to 24 months of age were considered missed opportunities for any dose of rotavirus vaccine according to the WHO recommendation.

Estimates of rotavirus vaccine coverage and missed opportunities were stratified by child and maternal demographic variables of interest available in the NIS dataset. Child demographic variables considered included age group, sex, race/ ethnicity, and number children in the household. Maternal demographics included age group, marital status, and education level. Socioeconomic variables and provider characteristics were also considered. Demographic characteristics were self-reported by respondents.

Statistical Analysis:

All analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina) and weights included in the NIS dataset. SAS procedures specific to complex survey methods were used to determine proportions, odds ratios, and associated confidence intervals included in this study, using appropriate weighting procedures and variables as described in the NIS Data User's Guide. Bivariate logistic regression was used to estimate odds ratios assessing rotavirus vaccine coverage and missed opportunities for rotavirus vaccination, and Wald confidence intervals were reported. Multivariable logistic regression that included covariables thought to be associated with rotavirus vaccination or missed opportunities was performed. (63, 64, 95)

Results

Rotavirus vaccine coverage

The 2014 NIS included 24,897 individuals. We excluded observations without provider-verified data (N = 9,838), or with a dose of rotavirus vaccine of unknown type (N = 488), resulting in 14,571 observations (59%) included in our analysis.

Among children 19-35 months of age in the 2014 NIS with provider-verified data, 71% of children were fully vaccinated, 15% were partially vaccinated, and 14% were unvaccinated. Among fully vaccinated children 72% received RV5 (RotaTeq®) and 27% received RV1 (RotaRix®). Less than 1% of fully vaccinated children received both rotavirus vaccines (mixed schedule). Among partially vaccinated children, 73% received 1 or 2 doses of RV5, 2% received a single dose of RV1, and 25% received 2 doses of vaccine, 1 dose of each type.

Rotavirus vaccine coverage varied by race, socioeconomic indicators, and provider characteristics in bivariate analysis (**Table 1**). Most notably, we found that children in households with ≥ 4 children were more than twice (2.3 times) as likely to be unvaccinated for rotavirus as children with fewer other children in the home. Children whose mothers were not college graduates were 40-90% more likely to be unvaccinated for rotavirus than children whose mothers were college graduates. Also, children who had been uninsured at any point were ~80% more likely to be unvaccinated for rotavirus than those who had uninterrupted insurance coverage. After controlling for race and ethnicity, children whose annual family income was below poverty were 50% more likely to be unvaccinated than those above poverty and $> \$75K$ (**Table 3**). When considering factors associated with partial rather than complete vaccination, race, mother's education, and the provider facility type were significantly associated with partial rather than complete rotavirus vaccination (**Table 1**). Children who did not receive vaccines from a private facility were significantly more likely to have been partially rather than fully vaccinated for rotavirus.

After controlling for income, the relationship between race and partial rather than complete rotavirus vaccination remained significant (**Table 3**).

Missed Opportunities up to 8 months of age- ACIP-recommended schedule

Most children unvaccinated for rotavirus (52%) had ≥ 1 missed opportunity for rotavirus vaccine initiation (DTaP received from 6-15 weeks of age). Among children unvaccinated for rotavirus, 72% had ≥ 1 ACIP-defined missed opportunity to receive rotavirus vaccine from 15 weeks to 8 months of age, 63% had ≥ 2 missed opportunities, and more than half (51%) had ≥ 3 missed opportunities (**Figure 1**). Among partially vaccinated children, 24% had ≥ 2 missed opportunities for rotavirus vaccination from 15 weeks to 8 months of age, and 14% had ≥ 3 missed opportunities. Overall, children were less likely to have a missed opportunity for rotavirus vaccination in a public healthcare facility than in a private healthcare facility. Children whose mothers were not college graduates were less likely to have missed opportunities for rotavirus vaccination than children whose mothers were college graduates. (**Table 2**). After controlling for income, black and multi-racial children were more likely to have ≥ 2 missed opportunities for rotavirus vaccination (**Table 3**).

Missed Opportunities up to 24 months of age- WHO- recommended schedule

Among children unvaccinated for rotavirus, 83% had ≥ 1 missed opportunity to receive rotavirus vaccine between 15 weeks and 24 months of age, 75% had ≥ 2 missed opportunities, and 69% had ≥ 3 missed opportunities (**Figure 1**). Among partially vaccinated children, 86% had ≥ 2 missed opportunities for rotavirus vaccination between 15 weeks and 8 months of age, and 61% had ≥ 3 missed opportunities. Vaccination at a public facility or hospital was associated with lower risk of missed opportunities than vaccination at a private healthcare facility (**Table 2**).

Sensitivity Analysis of Missed Opportunities and Potential Increases in Rotavirus Vaccine Coverage

We estimated the potential increase in rotavirus vaccine coverage that may be achieved by improving the linkage between DTaP and rotavirus vaccine administration (**Table 4**). We found that complete rotavirus vaccine coverage may be improved from 71% to 81% if all missed opportunities within the ACIP-recommended schedule were used. Additionally, we found that 97% complete coverage would be achievable if rotavirus vaccine were given simultaneously with DTaP or MMR through 24 months of age.

Discussion

Most children unvaccinated for rotavirus had at least one missed opportunity to receive rotavirus vaccine. We estimated a ~10% increase in complete rotavirus vaccination, or 81% coverage, if all missed opportunities for simultaneous DTaP and rotavirus vaccination within the ACIP schedule were used.

Healthy People 2020 states a target of 80% complete rotavirus vaccine coverage by year 2020. (65) Addressing missed opportunities for simultaneous rotavirus and DTaP vaccination may bridge the gap between current and target rotavirus vaccine coverage. Describing factors associated with missed opportunities for rotavirus vaccination is an important step towards improving uptake of rotavirus vaccines. We found that children who received vaccines from a private facility, and whose mothers had achieved a college degree were more likely to have missed opportunities for rotavirus vaccination before 8 months of age. Both provider attitudes and parental vaccine hesitancy have been previously associated with failure to vaccinate for rotavirus. (69, 72, 75)

Characteristics of children unvaccinated for rotavirus differed from those associated with missed opportunities to receive vaccine. While higher education and use of a private healthcare facility correlated with missed opportunities, lower educational achievement, uninsured status, and having ≥ 4 children in the household were strongly correlated with failure to receive rotavirus vaccine. This suggests that socio-ecological barriers play an important role in failure to receive rotavirus vaccine in the remaining ~20% of unvaccinated children.

Rotavirus vaccination is very effective in the prevention of severe gastroenteritis and failure to vaccinate has been clearly linked with risk for rotavirus disease. (4) Rotavirus disease in the U.S. has developed a biennial pattern since vaccine introduction, with the majority of disease occurring in “odd” years (e.g. 2009, 2011, 2013). The increase in rotavirus disease seen every other year may be attributable to dynamics of indirect protection. Since only ~70% of vaccine-eligible children in the U.S. are fully rotavirus vaccinated, it may take 2 years for a sufficient population of rotavirus-susceptible children to accumulate and amplify rotavirus transmission (as opposed to annual outbreaks before vaccine introduction). Interestingly, these biennial peaks of disease have not been observed in countries with higher rotavirus vaccine coverage. In Australia and Finland, where vaccine coverage is >90%, rotavirus disease prevalence remained low after vaccine introduction. (96, 97) Addressing underuse of rotavirus vaccine in the U.S. may eliminate the biennial surges of disease that occur.

Taking WHO recommendations into consideration, we explored possible rotavirus vaccine coverage if vaccine were given through 24 months of age. We found that linking rotavirus vaccination with DTaP or MMR vaccination through 24 months of age could increase rotavirus vaccine coverage up to 97%. Expanding the schedule for rotavirus vaccination would involve careful safety consideration. After the increased risk intussusception seen with RotaShield[®], vaccine policy-makers in the U.S. cautiously evaluated the safest ages for rotavirus vaccine administration. However, vaccinating older children against rotavirus may not only decrease rotavirus disease in the U.S., but also set an important precedent for global rotavirus vaccine use.

There are several limitations to our study. Use of survey data collected by random-digit-dialing may be a source of selection bias. Additionally, survey response error may impact the quality of our data; however, we attempted to minimize the possibility of inaccurate immunization history by including only children with provider-verified information. Use of weights and survey procedures may not accurately represent national immunization practices. Assumptions were made in order to simplify estimates, such as the assumption that children must receive three doses of RV5 to be completely vaccinated. Finally, we evaluated a single year of immunization data that may not adequately represent use of rotavirus vaccines in the U.S.

In conclusion, rotavirus vaccines are underused in the U.S. Low rotavirus vaccine uptake may be attributable not only to economic or logistical barriers, but also to vaccine hesitancy. Understanding the multi-faceted barriers to rotavirus vaccine uptake, and developing effective public health measures to promote vaccine use will be essential to reducing rotavirus morbidity in the U.S.

Table 1: Summary of rotavirus vaccination among children included in the 2014 National Immunization Survey, 19-35 months of age.

	%	Unvaccinated (%)	Partially vaccinated (%)	Fully vaccinated (%)	ORMH (95% CI) Unvaccinated vs. fully vaccinated	ORMH (95% CI) Unvaccinated vs. partially vaccinated	ORMH (95% CI) Partially vs. fully vaccinated
Child Demographics							
Race/ ethnicity	25.7	10.7	17.5	71.8	0.8 (0.6, 1.0)	0.5 (0.4, 0.7)	1.5 (1.2, 2.0)
Hispanic							
Non-Hispanic white	47.6	14.0	11.9	74.0	ref	ref	ref
Non-Hispanic black	13.6	17.5	25.0	57.5	1.6 (1.2, 2.1)	0.6 (0.4, 0.9)	2.7 (2.1, 3.5)
Non-Hispanic Multi-racial/other	13.1	16.4	13.2	70.4	1.2 (0.9, 1.6)	1.1 (0.7, 1.6)	1.2 (0.8, 1.6)
Number of children in household							
1	28.4	12.4	12.8	74.8	ref	ref	ref
2 or 3	56.4	12.6	14.9	72.5	1.1 (0.8, 1.3)	0.9 (0.6, 1.2)	1.2 (0.9, 1.6)
>= 4	15.2	21.6	21.7	56.7	2.3 (1.7, 3.1)	1.0 (0.7, 1.5)	2.2 (1.6, 3.1)
Maternal Demographics							
Age	0.7	22.1	15.2	62.7	1.9 (0.6, 6.2)	1.3 (0.3, 6.3)	1.5 (0.3, 6.8)
<=19 years							
20-29	42.0	14.4	19.9	65.7	1.2 (1.0, 1.5)	0.6 (0.5, 0.8)	1.9 (1.5, 2.3)
30+	57.3	13.5	12.0	74.5	ref	ref	ref
Marital status	63.1	13.5	12.8	73.7	ref	ref	ref
Married							
Not married	36.9	14.7	19.6	65.7	1.2 (1.0, 1.5)	0.7 (0.5, 1.0)	1.7 (1.4, 2.1)
Education	17.6	15.9	18.2	65.8	1.7 (1.3, 2.3)	0.7 (0.5, 1.0)	2.6 (1.9, 3.4)
< 12 Years	24.9	16.8	19.3	63.9	1.9 (1.5, 2.4)	0.7 (0.5, 0.9)	2.8 (2.2, 3.6)
12 Years							
> 12 Years, Non-college grad	23.9	13.4	18.4	68.2	1.4 (1.1, 1.8)	0.6 (0.4, 0.8)	2.5 (1.9, 3.3)
College grad	33.6	11.1	8.7	80.2	ref	ref	ref
Socioeconomic Characteristics							
Poverty status	27.4	10.7	7.3	82.0	0.7 (0.5, 0.8)	1.6 (1.2, 2.3)	0.4 (0.3, 0.6)
Above poverty, > \$75K							
Above poverty, <= \$75K	33.9	13.8	15.2	71.0	ref	ref	ref
Below poverty	33.4	16.8	21.9	61.4	1.4 (1.1, 1.8)	0.8 (0.6, 1.2)	1.7 (1.3, 2.1)
Unknown	5.4	*	*	*	*	*	*
Uninsured at any point	9.4	19.3	18.4	62.3	1.8 (1.3, 2.5)	1.3 (0.9, 1.9)	1.4 (1.0, 2.0)
Yes							
No	89.8	12.3	15.0	72.7	ref	ref	ref
Unknown	0.7	*	*	*	*	*	*
Provider Characteristics							
Provider facility type	11.7	15.7	19.2	65.1	1.6 (1.2, 2.2)	0.9 (0.6, 1.7)	1.8 (1.3, 2.6)
All public facilities							
All hospital facilities	12.6	19.5	14.9	65.6	2.0 (1.5, 2.5)	1.4 (1.0, 2.0)	1.4 (1.1, 1.8)
All private facilities	55.7	11.5	12.3	76.1	ref	ref	ref
Military/ other	3.1	15.5	22.5	62.1	1.6 (0.7, 3.7)	0.7 (0.3, 2.0)	2.1 (1.6, 2.7)
Mixed	16.8	12.1	22.3	65.6	1.2 (0.9, 1.6)	0.6 (0.4, 0.8)	2.2 (1.2, 4.3)

Table 2: Summary of missed opportunities for rotavirus vaccination among children included in the 2014 National Immunization Survey, 19-35 months of age.

	%	Missed opportunity 8m 0d (%)	2+ Missed opportunities 8m 0d (%)	Missed opportunity 24m 0d (%)	2+ Missed opportunities 24m 0d (%)	OR _{MH} (95% CI) Missed opportunity vs. none, 8m 0d	OR _{MH} (95% CI) Missed opportunity vs. none, 24 months	OR _{MH} (95% CI) Missed opportunity vs. none, 24 months
Child Demographics								
Race/ ethnicity								
Hispanic	25.7	69.1	11.3	78.9	73.8	0.9 (0.8, 1.1)	1.0 (0.8, 1.3)	1.0 (0.8, 1.2)
Non-Hispanic white	47.6	70.9	13.6	78.7	74.7	ref	ref	ref
Non-Hispanic black	13.6	65.7	19.2	79.0	74.5	0.8 (0.6, 1.0)	1.6 (1.2, 2.2)	1.0 (0.8, 1.2)
Non-Hispanic Multi-racial/other	13.1	68.1	16.5	76.2	72.5	0.9 (0.7, 1.1)	1.2 (1.0, 1.6)	0.9 (0.7, 1.1)
Number of children in household								
1	28.4	69.9	15.4	75.9	72.4	ref	ref	ref
2 or 3	56.4	69.2	12.8	78.4	74.2	1.0 (0.8, 1.2)	0.8 (0.7, 1.0)	1.1 (0.9, 1.3)
>= 4	15.2	69.2	16.8	83.5	77.2	1.0 (0.8, 1.2)	1.2 (0.9, 1.7)	1.3 (1.0, 1.6)
Maternal Demographics								
Age								
<=19 years	0.7	75.6	23.8	87.2	84.5	1.2 (0.4, 3.1)	1.8 (0.6, 5.9)	1.7 (0.7, 4.3)
20-29	42.0	64.8	13.2	76.7	71.4	0.7 (0.6, 0.8)	0.9 (0.7, 1.1)	0.8 (0.7, 1.0)
30+	57.3	72.6	14.7	79.6	76.0	ref	ref	ref
Marital status								
Married	63.1	71.9	14.0	79.3	75.1	ref	ref	ref
Not married	36.9	65.2	14.5	77.0	72.5	0.7 (0.6, 0.9)	1.0 (0.8, 1.3)	0.9 (0.7, 1.0)
Education								
< 12 Years	17.6	64.8	13.1	77.7	72.2	0.6 (0.5, 0.7)	0.9 (0.7, 1.2)	0.8 (0.7, 1.1)
12 Years	24.9	66.7	15.3	77.2	71.9	0.7 (0.5, 0.8)	1.1 (0.9, 1.4)	0.7 (0.6, 0.8)
> 12 Years, Non-college grad	23.9	67.2	13.2	77.3	71.4	0.7 (0.6, 0.8)	0.9 (0.7, 1.2)	0.8 (0.7, 1.0)
College grad	33.6	75.4	14.6	80.6	78.8	ref	ref	ref
Socio-economic Characteristics								
Poverty status								
Above poverty, > \$75K	27.4	74.2	12.9	78.8	77.1	1.2 (1.0, 1.5)	0.8 (0.7, 1.0)	1.0 (0.9, 1.3)
Above poverty, <= \$75K	33.9	70.4	15.4	78.0	73.5	ref	ref	ref
Below poverty	33.4	65.1	14.2	79.1	72.9	0.8 (0.7, 0.9)	1.0 (0.8, 1.2)	1.1 (0.9, 1.3)
Unknown	5.4	64.9	12.4	75.5	70.8	0.8 (0.6, 1.1)	0.8 (0.5, 1.2)	0.9 (0.6, 1.2)
Uninsured at any point								
Yes	9.4	63.5	12.5	76.3	68.5	0.7 (0.5, 0.9)	0.9 (0.6, 1.2)	0.8 (0.6, 1.2)
No	89.8	70.9	14.2	79.2	75.6	ref	ref	ref
Unknown	0.7	*	*	*	*	*	*	*
Provider Characteristics								
Provider facility type								
All public facilities	11.7	62.2	17.0	72.7	68.4	0.6 (0.5, 0.8)	1.4 (1.0, 1.9)	0.6 (0.5, 0.9)
All hospital facilities	12.6	58.6	10.7	69.3	65.5	0.5 (0.4, 0.6)	0.7 (0.6, 1.0)	0.5 (0.4, 0.7)
All private facilities	55.7	73.3	13.9	80.8	77.2	ref	ref	ref
Military/ other	3.1	75.1	13.6	89.5	79.6	0.9 (0.7, 1.1)	1.3 (1.0, 1.6)	1.2 (0.9, 1.5)
Mixed	16.8	71.6	16.5	83.1	76.8	1.1 (0.7, 1.8)	1.0 (0.4, 2.3)	2.0 (1.3, 3.2)

Table 3: Rotavirus vaccination and missed opportunities- multivariable analysis.

	Unvaccinated vs. fully vaccinated	Unvaccinated vs. partially	Partially vs. fully	ACIP Missed opportunities - 1+	ACIP Missed opportunities - 2+	WHO Missed opportunities - 1+	WHO Missed opportunities - 2+
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Hispanic	0.6 (0.5, 0.8)	0.6 (0.4, 1.8)	1.1 (0.8, 1.4)	1.1 (0.9, 1.3)	0.8 (0.6, 1.0)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)
Black	1.3 (0.9, 1.7)	0.7 (0.5, 0.9)	1.9 (1.4, 2.6)	0.9 (0.7, 1.1)	1.4 (1.1, 2.0)	1.0 (0.8, 1.3)	1.1 (0.9, 1.3)
Multi-racial	1.2 (0.9, 1.5)	1.1 (0.7, 1.6)	1.1 (0.8, 1.5)	0.9 (0.7, 1.1)	1.3 (1.0, 1.6)	0.9 (0.7, 1.1)	0.9 (0.7, 1.2)
White	ref	ref	ref	ref	ref	ref	ref
Above poverty, >\$75K	0.6 (0.5, 0.8)	1.5 (1.1, 2.1)	0.4 (0.3, 0.6)	1.2 (1.0, 1.5)	0.8 (0.7, 1.0)	1.1 (0.9, 1.3)	1.2 (1.0, 1.5)
Above poverty, <=\$75K	ref	ref	ref	ref	ref	ref	ref
Below poverty	1.5 (1.2, 1.9)	1.0 (0.7, 1.3)	1.6 (1.2, 2.1)	0.8 (0.7, 0.9)	0.9 (0.7, 1.2)	1.1 (0.9, 1.3)	1.0 (0.8, 1.2)

Table 4: Sensitivity analysis of rotavirus vaccine coverage given conditions of increased rotavirus vaccine use among children with missed opportunities to receive vaccine*

		ACIP- rotavirus vaccination through 8m of age			WHO- rotavirus vaccination through 24m of age		
	% Children with missed opportunities used	Additional % fully vaccinated	% Fully vaccinated	% Children with missed opportunities used	Additional % fully vaccinated	% Fully vaccinated	
Unvaccinated children (13.9%)	0	-	70.70	0	-	70.70	
	10	0.72	71.42	10	0.96	71.66	
	25	1.79	72.49	25	2.40	73.10	
	50	3.58	74.28	50	4.80	75.50	
	75	5.36	76.06	75	7.19	77.89	
	100	7.15	77.85	100	9.59	80.29	
Partially vaccinated children (15.3%)	0	-	70.70	0	-	70.70	
	10	0.36	71.06	10	1.31	72.01	
	25	0.90	71.60	25	3.29	73.99	
	50	1.80	72.50	50	6.57	77.27	
	75	2.70	73.40	75	9.86	80.56	
	100	3.60	74.30	100	13.15	83.85	
Overall	0	-	70.70	0	-	70.70	
	10	1.08	71.78	10	2.27	72.97	
	25	2.69	73.39	25	5.68	76.38	
	50	5.38	76.08	50	11.37	82.07	
	75	8.06	78.76	75	17.05	87.75	
	100	10.75	81.45	100	26.64	97.34	

* For sensitivity analysis, complete vaccination was considered 3+ doses and partial vaccination was considered 1-2 doses.

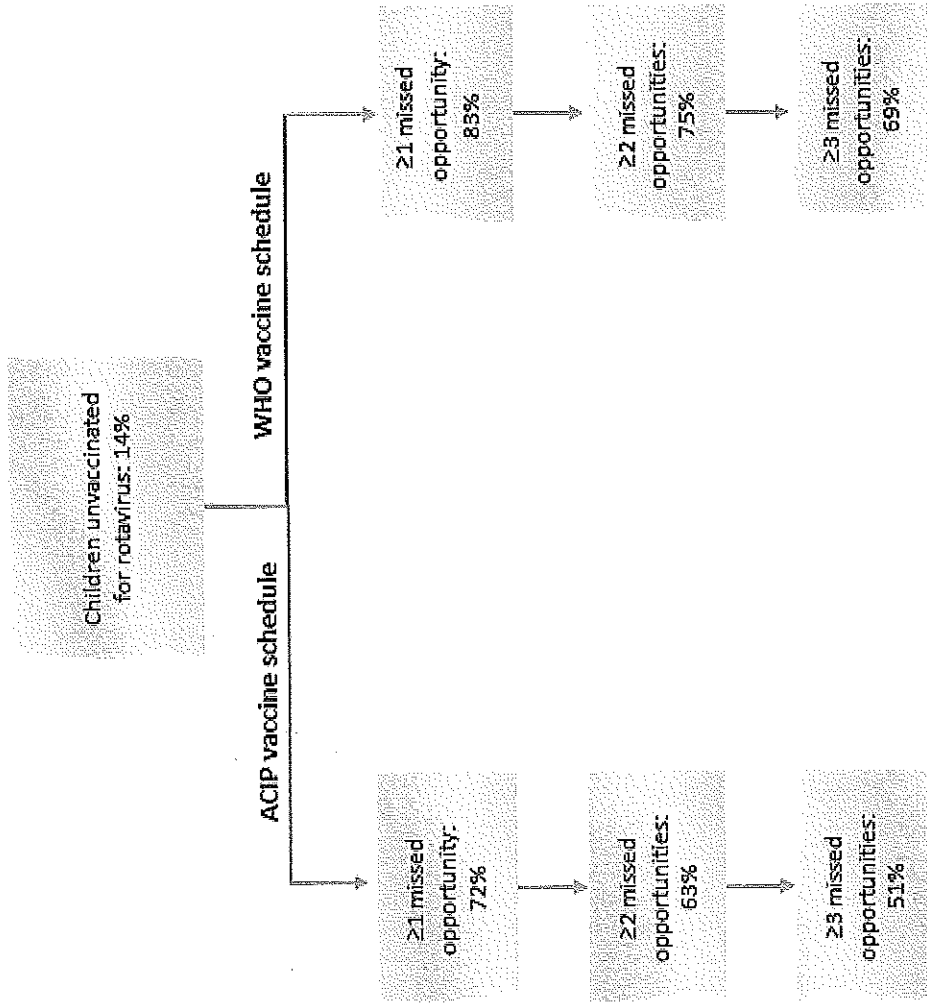


Figure 1: Flowchart of missed opportunities for rotavirus vaccination among children included in the 2014 National Immunization Survey, 19-35 months of age

Chapter III: Summary, Public Health Implications, Possible Future Directions

Rotavirus vaccines have dramatically decreased the occurrence of severe gastroenteritis in the U.S.; however, available vaccines are underused. Increasing use of licensed rotavirus vaccines in the U.S. would likely impact the residual vaccine-preventable burden of disease, perhaps diminishing the bi-seasonal surges of rotavirus disease that developed after vaccine introduction. Taking advantage of missed opportunities for simultaneous rotavirus and DTaP vaccination from 6 weeks through 8 months of age could increase rotavirus vaccine coverage by ~10%, allowing achievement of Healthy People 2020 target rotavirus vaccine coverage. Since most children who are unvaccinated for rotavirus had a missed opportunity to receive rotavirus vaccine simultaneously with other childhood vaccinations, influencing provider attitudes towards rotavirus vaccination may be an important step towards linking rotavirus and DTaP/ PCV vaccine coverage. There is limited information available regarding provider or parental attitudes towards rotavirus vaccination in the U.S., and most studies available are out of date. Identifying the current beliefs or attitudes that prevent providers from use of rotavirus vaccines may be an important step towards developing public health measures to encourage use of rotavirus vaccines.

In 2013, WHO recommended a more flexible rotavirus vaccination schedule that allows receipt of the first dose of rotavirus vaccine up to 24 months of age. Expanding the age for initiation was intended to encourage vaccination globally, particularly in regions where rotavirus vaccine initiation is not feasible between 6 and 15 weeks of age. (2, 88)

Vaccinating for rotavirus through 24 months of age in the U.S. could considerably increase use of rotavirus vaccines. We found that if rotavirus vaccines were administered simultaneously with DTaP or MMR through 24 months of age, 97% rotavirus vaccine coverage may be possible. Expanding the age for rotavirus vaccination in the U.S. would also set an important global precedent, since vaccine policies in the U.S. often have international impact. However, safety concerns, particularly related to intussusception, may prohibit consideration of rotavirus vaccination through 24 months of age.

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