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Halle Getachew **Date**

Rotavirus Vaccines and Health Care Utilization for Rotavirus and Diarrhea in the United States (2007-2014)

BY

Halle Getachew

Degree to be awarded: M.P.H.

Epidemiology

Thesis Committee Chair: Benjamin Lopman, PhD, MSc

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University in partial fulfillment of the requirements
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2016

Abstract

Rotavirus Vaccines and Health Care Utilization for
Rotavirus and Diarrhea in the United States (2007-2014)
By
Halle Getachew

In the United States, prior to the introduction of rotavirus vaccine in 2006, rotavirus caused an estimated 20 to 60 deaths, 55,000 to 70,000 hospitalizations, 205,000 to 272,000 emergency department visits, and 410,000 outpatient visits annually. There are two rotavirus vaccines currently available in the United States: RotaTeq (RV5) and Rotarix (RV1).

METHODS: This was a retrospective cohort study using data from the 2001-2014 Truven Health Marketscan Commercial Claims and Encounters Database, with commercially insured US children under 5 years of age. We assessed annual RV5 and RV1 rotavirus vaccine coverage and compared rates of diarrhea-associated health care utilization in prevaccine (2001–2006) versus post-vaccine introduction (2007–2014) years. We also examined vaccine effectiveness (VE) and duration of protection by comparing rates of diarrhea-associated health care utilization in vaccinated versus unvaccinated children.

RESULTS: In the cohort of > 308,000 children <5 years of age, 69% had received at least 1 dose of RV5 and 13% had received at least 1 dose of RV1 by December 31, 2013. Compared with the average rate of rotavirus-coded hospitalizations in the prevaccine years (2001–2006), rates were reduced by 75% in 2007–2008, 60% in 2008–2009, 94% in 2009–2010, 80% in 2010–2011, 97% in 2011–2012, 88% in 2012–2013, and 98% in 2013–2014. The overall, adjusted vaccine effectiveness estimates for RV5 were 87% (95% CI: 85%, 89%) among 3 to 11 months of age, 87% (95% CI: 85%, 89%) in 12 to 23 months of age, 88% (95% CI: 85%,90%) in 24 to 35 months of age and 88% (95% CI: 85%, 90%) in 36 to 47 months of age, and 88% (95% CI: 85%, 90%) in 48 to 59 months of age. The adjusted VE was 88% (95% CI: 80%, 93%) for RV1 among 3 to 11 months of age, 88% (95% CI: 79%, 93%) in 12 to 23 months of age and 88% (95% CI: 80%, 93%) in 24 to 35 months of age.

CONCLUSION: Implementation of rotavirus vaccines has substantially reduced rotavirus and diarrhea health care utilization in US children under 5 years of age.

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INTRODUCTION

In the United States, the introduction of the rotavirus vaccine in 2006 was associated with substantial reduction in rotavirus morbidity. Before the vaccine, rotavirus caused an estimated 20 to 60 deaths, 55,000 to 70,000 hospitalizations, 205,000 to 272,000 emergency department visits, and 410,000 outpatient visits annually [1,2]. There are two rotavirus vaccines currently available in the United States. The first pentavalent vaccine, RotaTeq (RV5) (Merck & Co., Inc. Whitehouse Station, New Jersey), was licensed on February 3, 2006. RV5 is composed of G1, G2, G3, G4 and P1 strains of rotavirus [3,6]. The Advisory Committee on Immunization Practices (ACIP) recommended that RV5 which is a 3 dose series should be administered orally at ages 2, 4, and 6 months of age. RV5 contained 5 attenuated reassortants developed from human and bovine hosts [3,6]. The second rotavirus vaccine, Rotarix (RV1) (GlaxoSmithKline Biologicals, Rixensart, Belgium), a monovalent vaccine was created from an attenuated human RV strain and licensed on April 3, 2008 [3,6]. RV1 contained G1, G3, G4 and G9 strains of rotavirus. ACIP recommended RVI be given orally as a 2 dose series at ages 2 months and 4 months. The upper age limit for the first-dose for both vaccines is 14 weeks and 6 days old, and the maximum age to receive the final dose is 8 months and 0 days of age. Both vaccines require a minimum of 4 week intervals between doses [2,3].

Previous studies using health insurance claims data from Truven Health Marketscan Commercial Claims and Encounters Database during 2007-2011 examined reductions in diarrhea associated health care utilization after the rotavirus vaccine was implemented. These analyses have found that after the implementation of rotavirus vaccines, diarrhea-associated health care utilization in US children significantly declined. In addition, the studies found both vaccines

provided protection against rotavirus hospitalization and RV5 offered durable protection through the fourth year of life [4,5]. We extend the previous work on Marketscan claims among children <5 years old by examining the most recently available administrative claims data to explore the long-term impact of RV5 and RV1. We had 3 specific objectives: 1) to assess rotavirus vaccine coverage; 2) to examine the total effects of rotavirus vaccination; and 3) to analyze vaccine effectiveness and duration of protection. We hypothesize that the current data from 2012-2014 rotavirus seasons will continue to show that rotavirus vaccine coverage is associated with reductions in rotavirus and diarrhea-related health care utilization in US children.

BACKGROUND

Rotavirus, which is part of the Reoviridae family, was first discovered in humans in 1973 [6,7]. Rotavirus is highly infectious and transmitted primarily via the fecal-oral route [6]. The virus causes gastroenteritis, vomiting and severe diarrhea that can lead to dehydration [6,7]. Other symptoms include fever and abdominal pain [6,7]. The infection in children has shown a range of outcomes varying from asymptomatic shedding, seizures, and even death [2,7]. Although there is no specific medication to treat rotavirus infection, there are treatments that can alleviate dehydration and other symptoms [2]. Infants and children under 5 years old are at risk for infection [6,7]. In particular, children in child care centers or other close contact settings have a higher risk [2,3]. The most severe rotavirus disease mainly affects unvaccinated children from 3 to 35 months of age [2,6].

Before the introduction of RV5 in 2006, rotavirus infection was the leading cause of severe diarrhea among children under 5 years of age in the US [6,7]. Furthermore, nearly all US children were infected with the virus before the age of 5[6,7,8]. Among those who became ill with the virus, 1 in 7 required a clinic or emergency department visit, 1 in 70 required

hospitalization, and 1 in 200,000 died [6,8]. The direct and indirect costs of rotavirus-related health care utilization was estimated to be approximately 1 billion annually [6,8]. In the pre-vaccine years, rotavirus infections had a distinct seasonal pattern [6]. Infections peaked in the winter and spring months, typically starting in the Southwest part of the country from November to December and spreading to the Northeast by April to May [6,9,10]. In the post-vaccine period the seasonal pattern changed and became less consistent [6,9,10].

The first rotavirus vaccine in the US, RotaShield (Rotashield, Wyeth Lederle Vaccines, USA) was licensed in August 1998 after a good pre-licensure efficacy. However, the vaccine was withdrawn in October 1999, after the vaccine was found to be associated with intussusception post-licensure. Intussusception, is a potentially serious intestinal blockage in which a segment of the intestine invaginates into another section of the intestine causing bowel obstruction [11]. Thus, the current vaccines RV5 and RV1 underwent a large clinical trial to evaluate both safety and efficacy. The clinical trial results for both vaccines showed no increased risk of intussusception in the US after vaccination [6,11,12]. Both vaccines have high efficacy in high-income countries against rotavirus. RV5 in a phase III trial conducted in the US and Finland demonstrated high efficacy of 74% (95% CI: 67%, 80%) against G1-G4 rotavirus gastroenteritis of any severity after 3 doses, and the efficacy was 98% (95% CI: 88%, 100%) against severe G1-G4 rotavirus gastroenteritis [6]. RV1 efficacy obtained from a randomized, double-blind placebo-controlled study in six European countries is 87% 95% CI: 80%, 92%) against any rotavirus gastroenteritis severity and 96% (95% CI: 90%, 99%) against severe rotavirus gastroenteritis in one rotavirus season [6].

In the US, the results from the real-world effectiveness studies using different methodologies for both vaccines are similar with efficacy data obtained from clinical

trials[6,13,14,15]. In a case-control study using the New Vaccine Surveillance Network (NVSN) data, vaccine effectiveness for RV5 was 83% (95% CI: 71%, 90%) against hospitalization and 77% (95% CI: 69%, 83%) against emergency department visits [13]. RV1 demonstrated 84% (95% CI: 53%, 94%) vaccine effectiveness against hospitalization and 79% (95% CI: 63%, 87%) against emergency department visits [13]. In a retrospective cohort study using MarketScan data, the vaccine effectiveness against rotavirus-coded hospitalization was 92% (95% CI: 87%, 96%) among RV5 recipients and 96% (95% CI: 74%, 100%) among RV1 recipients [5]. Furthermore, both vaccines have been found to reduce diarrhea-associated hospitalizations by 47% (95% CI: 46%, 49%) and emergency department visits by 22% (95% CI: 21%, 23%) [5]. Consistent with the MarketScan data studies, other studies using the National Respiratory and Enteric Viruses Surveillance System (NREVSS) have also shown that rotavirus seasonal peaks have shortened in the postvaccine period [4,5,6]. In addition, rotavirus vaccination has resulted in indirect protection (herd-immunity) among unvaccinated children. The MarketScan data showed rate reductions ranged from 50% (95% CI: 36%, 62%) in 2007-2008 to 25% (95% CI: 4%, 41%) in 2010-2011[5]. The same study reported 58% RV5 and 5% RV1 vaccine coverage for children under 5 years of age in 2010 [5].

METHODS

We conducted a retrospective cohort study using data from the 2001–2014 Truven Health MarketScan Commercial Claims and Encounters Database , with commercially insured US children <5 years of age. MarketScan data were extracted from insurance claims and contained de-identified, individual-level health care information from various public and private employer-sponsored health plans. The MarketScan database includes more than 100 million patients from over 100 insurance companies and these data come primarily from large employers; medium and

small firms are not represented [18]. Medicaid claims were not included in MarketScan database. All statistical analyses were performed using SAS 9.3 (Statistical Analysis Software).

We identified diarrhea-associated health care events using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes. The following ICD-9-CM codes were used to identify children with viral enteritis, 008.6–008.8 (including rotavirus, 008.61); bacterial enteritis, 001.0–005.9 (excluding 003.2) and 008.0–008.5; parasitic intestinal disease, 006.0–007.9 (excluding 006.3–006.6); presumed infectious diarrhea, 009.0–009.3; presumed noninfectious diarrhea, 558.9; and diarrhea not otherwise specified, 787.91. In addition to all-cause diarrhea events, rotavirus-specific events (008.61) were separately analyzed.

We classified healthcare setting events in 3 categories: hospitalizations, emergency department visits, and outpatient visits. An inpatient admission was defined as hospitalization if coded as the primary discharge diagnosis or listed in any of the 15 diagnosis categories from the inpatient-admission table. An outpatient visit was counted if specified in 1 of the 2 diagnosis fields in the outpatient-service table. Emergency department visit was included (i.e., not hospitalization or outpatient visit) if "urgent care facility" or "emergency room" was specified in either the inpatient-services table or the outpatient-services table.

RV5 and RV1 Coverage

Vaccine coverage was examined using data for the period of January 2006 to June 2014. Coverage was defined as receipt of at least 1 dose of RV5 or RV1 in a subgroup of children with continuous enrollment in 1 insurance plan from birth to at least 3 months of age. Children from states with universal vaccination programs that included rotavirus vaccine or where rotavirus vaccine inclusion in the universal vaccination program could not be determined were excluded

from the coverage evaluation because vaccination in those states were unlikely to have been billed to third-party payers and therefore would probably not be recorded in MarketScan database. During the period of 2007-2012, 13 states were excluded from the analysis: Alaska, Idaho, Massachusetts, Maine, North Dakota, New Hampshire, New Mexico, Oregon, Rhode Island, Vermont, Washington, Wisconsin, and Wyoming. In the 2013-2014 period, the following states were excluded: Connecticut, Idaho, Maine, Massachusetts, New Hampshire, New Mexico, Rhode Island, South Dakota, Vermont, Washington, and Wyoming.

Current Procedural Terminology (CPT) code 90680 was used to identify children who received RV5 and code 90681 for children who received RV1 among the eligible cohort. The coverage results were validated by comparing the proportion of children who had received at least 1 diphtheria-tetanus-acellular pertussis vaccine (DTaP) dose by 3 months of age in the MarketScan Database among the same cohort with the DTaP coverage from National Immunization Survey (NIS) reports. NIS program at the Centers for Disease Control and Prevention conducts surveys to observer vaccine coverage in children [19,20].

Total Effects of Rotavirus Vaccination

We examined the total effects of vaccination, which is the direct benefits of the vaccine in vaccinated children combined with the indirect benefits in unvaccinated children. Diarrhea-associated health care utilization rates were calculated for enrolled children < 5 years of age who were seen in inpatient, emergency departments, and outpatient settings. In addition, rotavirus-specific coded hospitalizations were also examined. Rates were calculated by the number of health care events per 10,000 person-years. We used the number of days each child was enrolled per calendar month and year of the study as the follow-up time in calculating utilization rates per

10,000 person-years of follow-up. We assessed the total effects of vaccination by comparing the same study population before and after vaccine introduction. Thus data from all states, including those with universal vaccination programs were included in the analysis of trends. Temporal trends of the diarrhea-associated healthcare utilization rate during the entire study period were evaluated. We also compared rotavirus-coded hospitalization and diarrhea-associated health care utilization rates during each of the post-vaccine years of 2007–2014 (July – June) with the annual mean rates during the 5-year pre-vaccine baseline period from July 2001–June 2006, according to age group (categorized: <1 year, 1 year, 2-4 years, and <5 years). Poisson regression was used to calculate rate reductions and 95% confidence intervals.

Vaccine Effectiveness and Duration of Protection from Rotavirus Vaccination

To examine direct vaccine benefits from RV5 and RV1, we compared rates of rotavirus-coded hospitalization and diarrhea-associated health care utilization among vaccinated versus age-eligible unvaccinated children by age group (categorized: 3–11 months, 12–23 months, 24–35 months, 36–47 months, and 48–59 months) at hospitalization for a diarrhea-associated event. A single child's diarrhea-associated health care event was restricted to one event per age group. All children who were age-eligible to receive RV5 or RV1 and who were continuously enrolled in their insurance plan for the entire time period were included. RV5 age-eligible children are those younger than the first dose upper limit of 14 weeks and 6 days when RV5 was licensed on February 3, 2006. RV1 age-eligible children are those younger than the first dose upper limit of 12 weeks (initial recommendation) when RV1 was licensed on April 3, 2008. Children from states with universal vaccination programs or those who had received mixed vaccine schedules with both RV1 and RV5 doses were excluded. Poisson regression was used to calculate rate ratio and 95% confidence intervals associated with RV5 or RV1 administration

adjusting for birth quarter[LB14] . The adjusted rate ratios were subtracted from 1 to obtain adjusted VE estimates.

RESULTS

Rotavirus-Vaccine Coverage

In the cohort of > 308,000 children <5 years of age from 39 states, 69% had received at least 1 dose of RV5 and 13% had received at least 1 dose of RV1 by December 31, 2013 (Table 1). Coverage for both vaccines increased gradually in all age groups. After RV5 licensure, coverage increased from 64% on December 31, 2007 to 72% on December 31, 2013 in children < 1 year old. In the same time period, coverage increased from 23% to 71% in 1 year old and 8% to 68% among 2-4 year old children. Similarly, after RV1 introduction, RV1 coverage continued to increase from 12% on December 31, 2009 to 16% by December 31, 2013 in < 1 year old, 1% to 15% in 1 year old and 0 to 11% in children 2 to 4 year old. In the same cohort using MarketScan data, the proportion of children who had received at least 1 DTaP dose by 3 months of age was 92%, in comparison to 88% coverage reported by NIS 2014 data.

Total Effects of Rotavirus Vaccination

There were 70,184 hospitalizations, 347,074 emergency department visits, and 2,654,266 outpatient visits associated with diarrhea among children <5 years of age in the Marketscan database. In the prevaccine years (2001-2006), the monthly diarrhea-associated health care utilization rates had an annual (seasonal) pattern with a sharp peak during February to March in all healthcare settings, which coincided with the seasonal pattern of rotavirus-coded hospitalization. However, in post-vaccine years, the monthly rotavirus-coded hospitalization and diarrhea-associated healthcare utilization rates in all settings substantially decreased and the

seasonal patterns changed. The peaks in all settings became less pronounced and flat compared to the prevaccine years. The results show the mean rate of all-diarrhea hospitalizations decreased from 51 in prevaccine to 29 (rate reduction: 65% (95% CI: 63%, 66%)) in post-vaccine per 10,000 person-years and similarly, rotavirus-coded hospitalizations rate declined from 13 to 3(rate reduction: 98% (95% CI: 97%, 98%)). We also found reductions in the mean rate when comparing the pre-vaccine versus post-vaccine for emergency department visits 178 to 156 (rate reduction: 29% (95% CI: 28%, 30%)) and 1347 to 1176 (rate reduction: 24% (95% CI: 24%, 25%)) in outpatient visits. In particular, the rotavirus-coded hospitalizations changed from annual peak to biennial peak (Figure 1). In post-vaccine, the mean annual rotavirus-coded hospitalizations rate per 10,000 person-year were higher in odd years (11.6 in 2007, 5.2 in 2009, 2.7 in 2011, and 2.0 in 2013) compared to even calendar years (3.7 in 2008, 0.9 in 2010, 0.5 in 2012 and 0.4 in 2014).

Annual rates of rotavirus-coded hospitalization among children < 5 years of age declined from a baseline of 14 hospitalizations per 10,000 person-year to 4 in 2007-2008, 6 in 2008-2009, 1 in 2009-2010, 3 in 2010-2011, 0.38 in 2011-2012, 2 in 2012-2013, and 0.49 hospitalizations per 10,000 person-year in 2013-2014. Similar declines were observed across age groups for rotavirus-coded hospitalizations. The annual rates of diarrhea-associated hospitalization in children < 5 year of age declined to 35 in 2007-2008, 39 in 2008-2009, 24 in 2009-2010, 27 in 2010-2011, 21 in 2011-2012, 24 in 2012-2013 and 18 in 2013-2014 from the baseline rate of 52 per 10,000 person-year. Furthermore, declines were also observed in diarrhea-associated emergency visits and outpatient visits in children under 5 years of age (Table 1).

Compared with prevaccine years (2001-2006), significant reductions in rotavirus-coded hospitalization rates were observed in all 7 post-vaccine years among all age groups. Compared

with the average rate of rotavirus-coded hospitalizations in the prevaccine years (2001–2006), rates were reduced by 75% in 2007–2008, 60% in 2008–2009, 94% in 2009–2010, 80% in 2010–2011, 97% in 2011–2012, 88% in 2012–2013, and 98% in 2013–2014 in children under the age of 5. We also observed that, as vaccine coverage grew, the overall rate reduction in rotavirus-coded hospitalization also increased. However, high rate reductions were still present despite low vaccine coverage in some age groups and years (Table 1).

In the post-vaccine years, significant reductions were recorded in diarrhea-associated hospitalization among children <5 years of age. Compared with the average rate of diarrhea-associated hospitalizations in the prevaccine years, rates were reduced by 33% in 2007–2008, 25% in 2008–2009, 54% in 2009–2010, 47% in 2010–2011, 60% in 2011–2012, 53% in 2012–2013, and 65% in 2013–2014 in children under the age of 5. The annual rate reduction varied more widely in diarrhea-associated emergency visits and outpatient visits in each age group and year. The highest reduction for both health care settings among <5 years of age was observed in 2014: 29% (95% CI: 28%, 30%) emergency visits and 24% (95% CI: 24%, 25%) in outpatient (Table 1).

Table 1 Annual Rates of Rotavirus-Coded and Diarrhea-Associated Health Care Utilization Among Children <5 Years of Age Before and After Rotavirus-Vaccine Introduction by Age Group and Health Care Setting

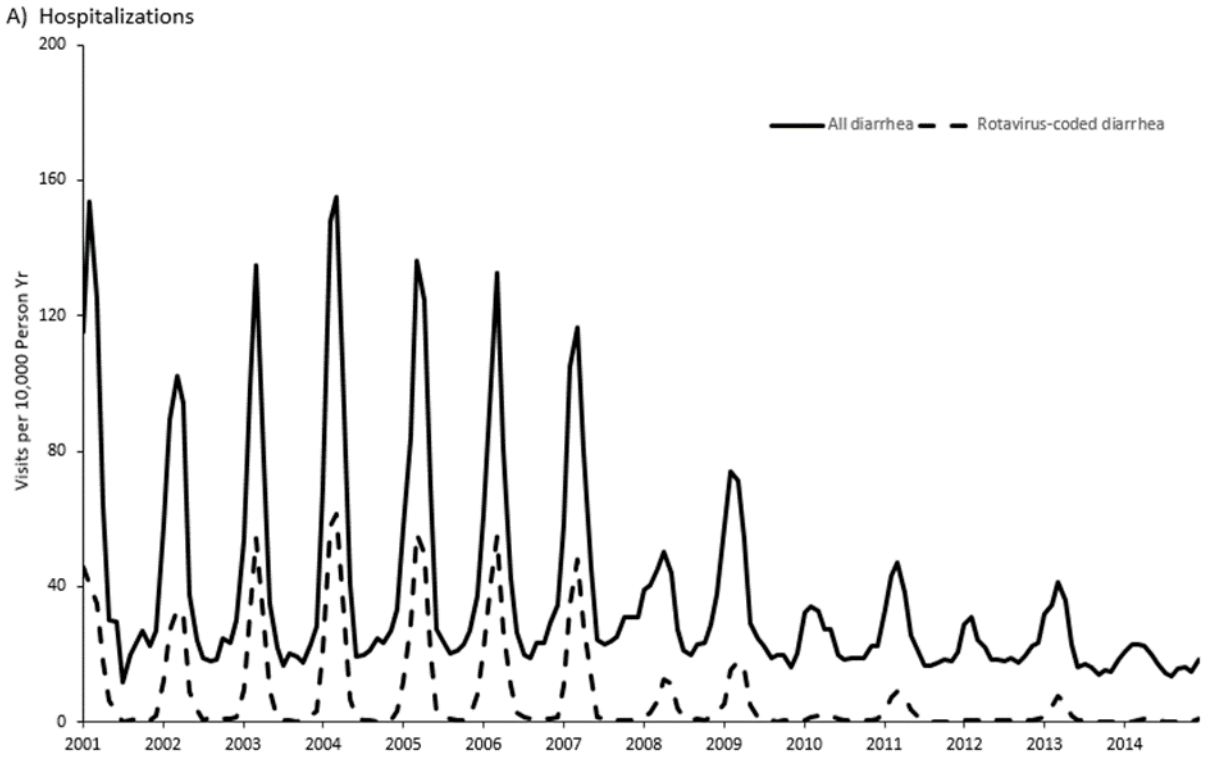
Age Group	Coverage		Rotavirus-Coded Hospitalizations		Diarrhea-Associated Hospitalizations		Diarrhea-Associated ED Visits		Diarrhea-Associated Outpatient Visits	
	RV5[a]	RV1[b]	Rate, n/ 10,000 PY	Rate Reduction (95% CI), %	Rate, n/ 10,000 PY	Rate Reduction (95% CI), %	Rate, n/ 10,000 PY	Rate Reduction (95% CI), %	Rate, n/ 10,000 PY	Rate Reduction (95% CI), %
<1 year old										
2001-2006[c]	NA	NA	16	Ref.	65	Ref.	212	Ref.	1713	Ref.
2007-2008	64	NA	3	81 (77 to 84)	50	24 (20 to 27)	204	4 (1 to 6)	1608	6 (5 to 7)
2008-2009	73	NA	4	78 (74 to 81)	45	30 (27 to 34)	185	13 (11 to 15)	1499	13 (12 to 13)
2009-2010	64	12	1	95 (93 to 96)	34	47 (45 to 50)	131	38 (37 to 40)	1197	30 (30 to 31)
2010-2011	68	10	2	88 (85 to 90)	36	45 (43 to 48)	140	34 (32 to 36)	1211	29 (29 to 30)
2011-2012	67	15	0	98 (96 to 98)	31	52 (49 to 54)	133	37 (36 to 39)	1158	32 (32 to 33)
2012-2013	70	15	1	91 (89 to 93)	34	48 (45 to 51)	151	29 (27 to 31)	1192	30 (30 to 31)
2013-2014	72	16	1	97 (95 to 98)	28	57 (54 to 59)	148	30 (29 to 32)	1196	30 (30 to 31)
1 year old										
2001-2006[c]	NA	NA	33	Ref.	96	Ref.	324	Ref.	2376	Ref.
2007-2008	23	NA	9	72 (69 to 76)	56	41 (38 to 44)	282	13 (11 to 15)	2265	5 (4 to 6)
2008-2009	64	NA	9	74 (71 to 77)	60	38 (35 to 41)	298	8 (6 to 10)	2355	1 (0 to 2)
2009-2010	72	1	1	96 (95 to 97)	35	64 (62 to 66)	198	39 (37 to 40)	1825	23 (23 to 24)
2010-2011	64	12	4	87 (85 to 89)	39	59 (57 to 61)	220	32 (30 to 34)	1933	19 (18 to 19)
2011-2012	68	10	1	98 (97 to 99)	28	71 (69 to 72)	184	43 (42 to 45)	1743	27 (26 to 27)
2012-2013	67	15	3	91 (89 to 92)	34	64 (62 to 66)	245	24 (23 to 26)	1943	18 (18 to 19)
2013-2014	71	15	0	99 (98 to 99)	23	76 (75 to 78)	197	39 (37 to 41)	1711	28 (27 to 29)
2-4 years old										
2001-2006[c]	NA	NA	8	Ref.	32	Ref.	130	Ref.	871	Ref.
2007-2008	0	NA	2	72 (67 to 76)	21	34 (31 to 37)	119	9 (7 to 11)	871	0 (-1 to 1)
2008-2009	8	NA	6	26 (19 to 32)	29	9 (5 to 13)	155	-19 (-21 to -17)	984	-13 (-14 to -12)
2009-2010	29	0	1	89 (87 to 91)	17	49 (46 to 51)	105	19 (17 to 21)	795	9 (8 to 9)
2010-2011	53	0	3	63 (59 to 67)	20	37 (35 to 40)	124	5 (3 to 7)	865	1 (0 to 1)
2011-2012	62	5	0	96 (95 to 97)	14	57 (55 to 59)	95	27 (25 to 28)	735	16 (15 to 16)
2012-2013	67	8	1	80 (77 to 83)	17	47 (44 to 49)	135	-4 (-6 to -2)	860	1 (0 to 2)
2013-2014	68	11	0	97 (96 to 98)	13	61 (59 to 63)	105	19 (18 to 21)	732	16 (15 to 17)
<5 years old										
2001-2006[c]	NA	NA	14	Ref.	52	Ref.	185	Ref.	1348	Ref.
2007-2008	17	NA	4	75 (72 to 77)	35	33 (31 to 35)	169	9 (7 to 10)	1303	3 (3 to 4)
2008-2009	32	NA	6	60 (58 to 63)	39	25 (23 to 27)	188	-2 (-3 to 0)	1360	-1 (-1 to 0)
2009-2010	45	3	1	94 (93 to 95)	24	54 (52 to 55)	128	31 (30 to 32)	1079	20 (20 to 20)
2010-2011	58	5	3	80 (78 to 81)	27	47 (46 to 49)	145	22 (21 to 23)	1139	16 (15 to 16)
2011-2012	64	8	0	97 (97 to 98)	21	60 (59 to 61)	120	35 (34 to 36)	1015	25 (24 to 25)
2012-2013	67	11	2	88 (86 to 89)	24	53 (52 to 54)	158	15 (13 to 16)	1134	16 (16 to 16)
2013-2014	69	13	0	98 (97 to 98)	18	65 (63 to 66)	132	29 (28 to 30)	1021	24 (24 to 25)

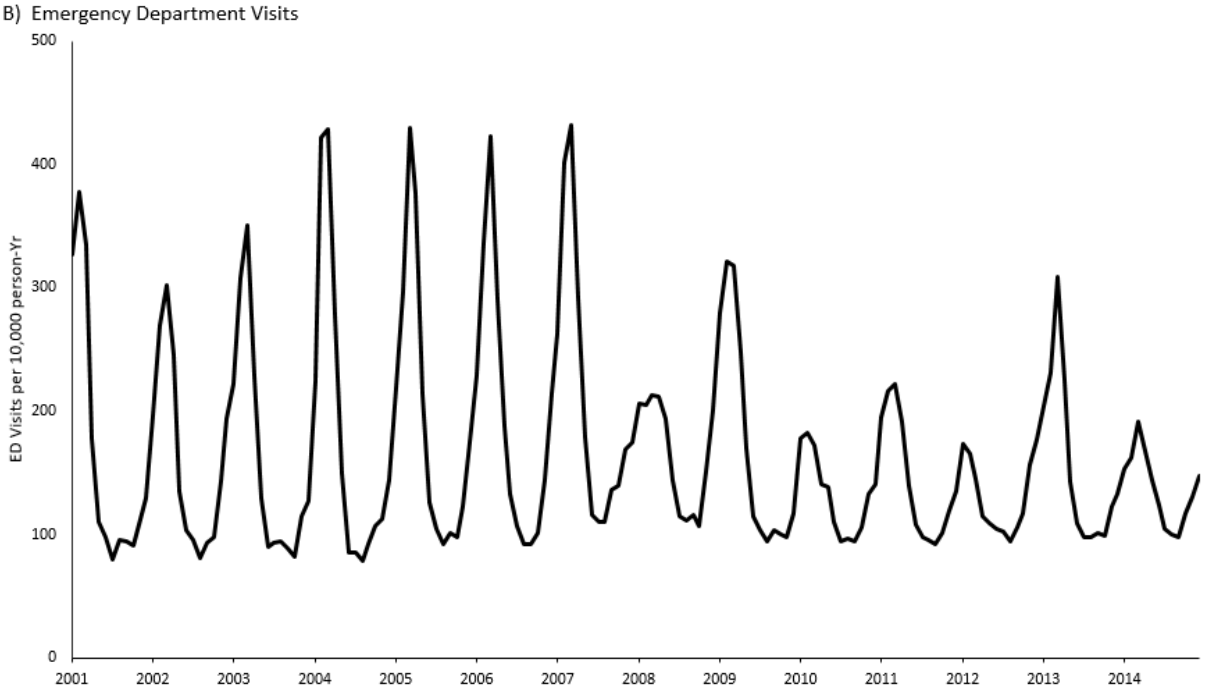
CI, confidence interval; ED, emergency department; NA not applicable; PY, person-year; reference group.

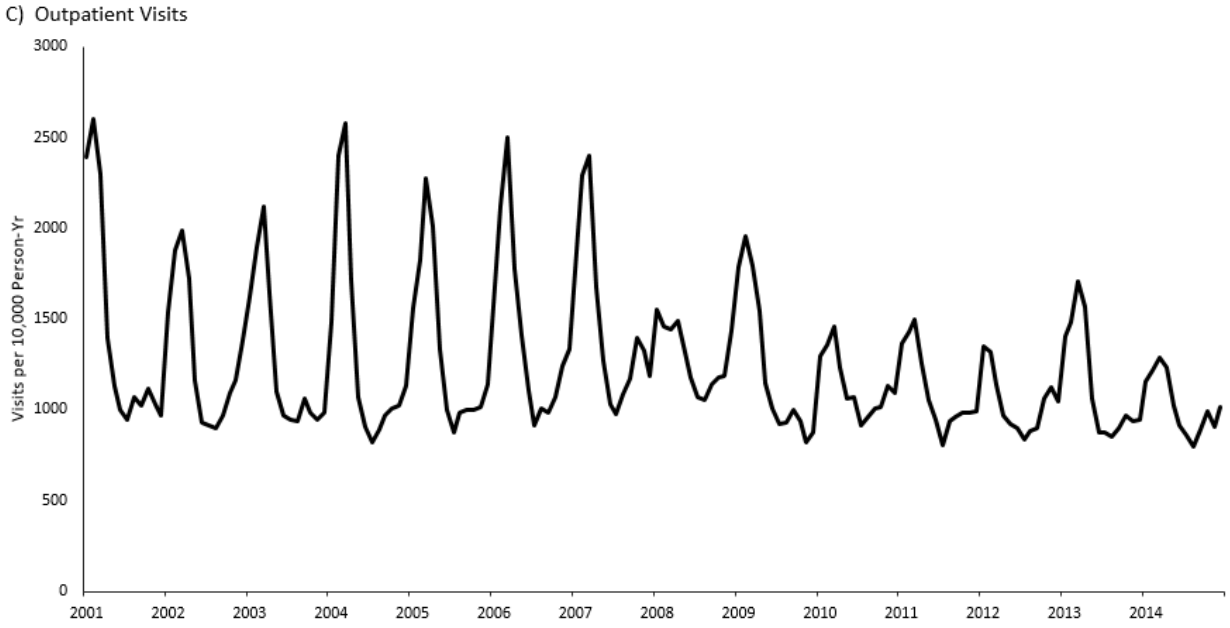
[a] Coverage was defined as receipt of at least 1 dose of RV5 by December 31, 2007; December 31, 2008; December 31, 2009; December 31, 2010; December 31, 2011; December 31, 2012; December 31, 2013, in children who had been in the database since birth and for at least 3 month continuously enrolled. Coverage for children <1 year of age was restricted to those who were eligible for vaccination (i.e., children 3-11 months).

[b] Coverage was defined as receipt of at least 1 dose of RV1 by December 31, 2009; December 31, 2010; December 31, 2011; December 31, 2012; December 31, 2013, in children with the same criteria as defined for RV5 coverage. Because RV1 was not introduced until April 2008, coverage of RV1 begins with the first full season starting 2009.

[c] For 2001-2006, the average annual rate for the time period is shown.


A) Hospitalizations
All diarrhea
Rotavirus-coded diarrhea
Visits per 10,000 Person Yr
200
160
120
80
40
0
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014


B) Emergency Department Visits
ED Visits per 10,000 person-Yr
500
400
300
200
100
0
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014



Vaccine Effectiveness and Duration of Protection from Rotavirus Vaccination

RV5 adjusted VE was 87% (95% CI: 85%, 89%) against rotavirus-coded hospitalization among 3 to 11 months of age, 87% (95% CI: 85%, 89%) in 12 to 23 months of age, 88% (95% CI: 85%, 90%) in 24 to 35 months of age, 88% (95% CI: 85%, 90%) in 36 to 47 months of age, and 88% (95% CI: 85%, 90%) in 48 to 59 months of age. RV1 adjusted VE was 88% (95% CI: 80%, 93%) against rotavirus-coded hospitalization among 3 to 11 months of age, 88% (95% CI: 79%, 93%) in 12 to 23 months of age and 88% (95% CI: 80%, 93%) in 24 to 35 months of age (Table 2). Due to low rates of rotavirus-coded hospitalization rates among children in 36-47 and 48-59 months of age, VE estimates could not be calculated.

We observed significant VE estimates against diarrhea-associated hospitalizations and emergency visits in vaccinated children with little variation among age groups. RV5 adjusted VE

estimates ranged from 42% (95% CI: 40%, 45%) against diarrhea-associated hospitalizations in 3 to 11 months of age to 43% (95% CI: 40%, 46%) in 48-59 months of age. Similar VE estimates were seen among those vaccinated with RV1. RV1 adjusted VE was 40% (95% CI: 34%, 45%) against diarrhea-associated hospitalizations among 3 to 11 months of age and 43% (95% CI: 35%, 51%) in 24 to 35 months of age. Furthermore, the adjusted VE estimates ranged from 23% to 24% against diarrhea-associated emergency department visits from RV5 and for RV1 the adjusted VE ranged from 21% to 26%. However, we did not detect any significant reduction in diarrhea-associated outpatient visits for both vaccines.

Table 2) Vaccine Effectiveness (VE) and Duration of Protection among Children Who Received at Least 1 Dose of RV5 or RV1 Versus Unvaccinated Children by Age [a]

Age (months) [d]	Health Care Utilization Rate, n/10,(RV5	Unvaccinated[b]	VE (95% CI), %	Health Care Utilization Rate, n/10, RV1	Unvaccinated[c]	VE (95% CI), %
Rotavirus-Coded Hospitalizations						
3-11	0.93	6.96	87 (85 to 89)	0.69	5.05	88 (# to #)
12-23	1.60	17.25	87 (85 to 89)	0.72	11.21	88 (# to #)
24-35	1.12	9.34	88 (85 to 90)	1.90	7.38	88 (# to #)
36-47	0.15	4.24	88 (85 to 90)	0.00	3.88	NA
48-59	0.42	3.59	88 (85 to 90)	0.00	3.18	NA
Diarrhea- Associated Hospitalizations						
3-11	41	61	42 (40 to 45)	40	59	40 (# to #)
12-23	60	107	42 (40 to 45)	63	107	40 (# to #)
24-35	35	66	43 (40 to 45)	39	76	41 (# to #)
36-47	31	42	42 (39 to 44)	62	48	42 (# to #)
48-59	22	59	43 (40 to 46)	13	98	43 (# to #)
Diarrhea-Associated Emergency Departm						
3-11	201	227	23 (21 to 24)	209	218	21 (# to #)
12-23	355	460	23 (22 to 25)	398	493	21 (# to #)
24-35	235	291	24 (23 to 26)	296	342	25 (# to #)
36-47	173	203	24 (23 to 26)	168	262	24 (# to #)
48-59	140	153	25 (23 to 27)	95	211	26 (# to #)
Diarrhea-Associated Outpatient Visits						
3-11	1520	1293	-4 (-5 to -3)	1529	1244	-7 (-9 to -6)
12-23	2683	2568	-4 (-5 to -3)	2996	2787	-7 (-8 to -5)
24-35	1634	1552	-3 (-4 to -2)	1863	1790	-4 (-6 to -3)
36-47	1097	1180	-2 (-3 to -1)	1366	1534	-4 (-6 to -2)
48-59	896	896	-1 (-2 to 0)	1198	1262	-3 (-5 to -1)

NA, not applicable; PY, person-year; CI, confidence interval

[a] Vaccination status was determined by the presence or absence of a current procedural terminology code for receipt of at least 1 dose of RV5. Children who were either from states with universal vaccination programs or had received mixed vaccine schedules with both RV1 and RV5 doses were excluded.

[b] Children who were age-eligible for the RV5 vaccine as of February 3, 2006, when RV5 was first recommended (ie, age less than the first-dose upper limit of 14 wk and 6 d when RV5 was licensed on February 3, 2006) and who were continuously enrolled in their insurance plan for at least 3 mo.

[c] Children who were age-eligible for the RV1 vaccine as of April 3, 2008, when RV1 was first recommended (ie, age less than the first-dose upper limit of 12 wk (previous recommendation) when RV1 was licensed on April 3, 2008) and who were continuously enrolled in their insurance plan for at least 3

[d] Age at hospitalization for a diarrhea-associated event.

DISCUSSION

Key Findings

The findings of our study using MarketScan data with commercially insured children under 5 years of age, support our hypothesis that rotavirus vaccines reduced rotavirus-coded and diarrhea-related health care utilization in US children. We also observed both vaccines provide strong and enduring protection against rotavirus-coded hospitalizations in children up to 5 years of age. The two vaccines demonstrate high effectiveness and continue to reduce the disease burden in US children.

Rotavirus vaccine coverage, though modest, has increased steadily over the years. By the end of 2013 coverage had reached 82% of children under 5 years of age and 88% coverage among less than 1 year old. However, the rotavirus coverage was still about 11% lower than DTaP coverage for the same cohort in MarketScan data (table 1). RV1 vaccine introduced 2 years later than RV5, had significantly lower coverage as compared with RV5 coverage in all age groups.

We observed declines in rates of rotavirus-coded and diarrhea-associated hospitalizations, emergency department visits and outpatient visits in US children under 5 years of age over the seven post-vaccine rotavirus seasons. In the post-vaccine years, rate reductions for rotavirus-coded hospitalization ranged from 60% in 2008–2009 to 98% in 2013–2014. Greater declines observed in the later years were associated with greater vaccine coverage. Furthermore, after rotavirus vaccination, diarrhea-associated hospitalizations also declined by 65% in 2013-2014, during the same season emergency department visits declined by 29% and outpatient visits declined by 24%. These results strongly suggest that reductions in rotavirus-coded

hospitalization and diarrhea-associated healthcare utilization were due to rotavirus vaccination, and not because of unmeasured extraneous factors.

We found both RV1 and RV5 to be highly effective against rotavirus hospitalizations and both vaccines provide similar protection. The birth-quarter adjusted VE estimates were similar across all 5 age groups for both vaccines. The level of protection obtained from both RV5 and RV1 vaccination against rotavirus-specific hospitalization were persistent through the fourth year of life, with no evidence of waning immunity.

Relation to Other Studies

This study also supports the findings of previous research studies using MarketScan data that recorded reduction in rotavirus-coded hospitalization and diarrhea-associated hospitalization, emergency department visits and outpatient visits [4,5]. The study underscored the importance of rotavirus vaccination against rotavirus-coded hospitalization and diarrhea-associated healthcare utilization. Significant reductions in emergency department visits were also reported in a study using State Emergency Department databases [16]. Other studies using the New Vaccine Surveillance Network (NVSN) data and data from 3 hospitals in Georgia and Connecticut have shown that both vaccines have high effectiveness and provide lasting protection [13,14,15,17].

Limitations

There were some limitations with this study. First, our analysis only included insured children. Uninsured children and children on Medicaid were not captured. The data did not include information on ethnicity/race or socioeconomic status. Additionally, MarketScan claims data typically come from large employers, therefore, small firms were not well represented.

Second, states with universal vaccination programs were not included in the total effects and vaccine effectiveness analysis. We restricted 13 states in 2007 to 2013 and only 11 states in 2013 and 2013. However, it is possible we did not capture all the vaccinated children during this transition year. Third, the analysis only adjusted for birth-quarters, we did not control for all other possible confounders. We are not aware of other factors in this study that could potentially influence rotavirus vaccine coverage in children. Fourth, rotavirus cases were identified based on the appearance of an ICD-9 diagnosis code for rotavirus on health care claims, therefore the validity of the results depend on the accuracy and consistency of physician-assigned diagnosis of rotavirus and the diagnostic coding. A study conducted in two hospitals, found not all acute gastroenteritis hospitalizations among children <5 were routinely tested for rotavirus and of those tested a large proportion were positive [21]. There are inconsistencies in rotavirus laboratory testing and coding across all healthcare settings, particularly testing for rotavirus was not common in emergency department visits and outpatient visits [4,5,16]. Therefore, we were not able to assess rotavirus-coded emergency department visits and rotavirus-coded outpatient visits.

Recommendations & Conclusion

Future studies should consider examining rotavirus vaccination coverage and health care utilization by regional and socioeconomic differences. In addition, the indirect effects of vaccination by examining unvaccinated children should be considered. High reductions in health care utilization were seen despite lower coverage in some age group and years, thereby conferring indirect protection. Lastly, future studies can consider cost savings associated with the reduction in health care utilization.

In conclusion, since the implementation of rotavirus vaccination program, rotavirus hospitalizations, and diarrhea-related health care utilization have declined dramatically among US children under 5 years of age. Both rotavirus vaccines provide a strong and durable protection against rotavirus hospitalizations.

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