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Rotavirus Vaccination and Short-term Risk of Adverse Events in US Infants

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Abstract

Background—To evaluate the short-term risk of adverse events associated with rotavirus vaccine (RV) in infants, overall and by vaccine formulation (3-dose pentavalent, RV5; 2-dose monovalent, RV1).

Methods—We identified US newborns with commercial insurance during 2006–2014 receiving a diphtheria-tetanus-pertussis vaccine (DTaP) dose and assessed if RV was administered concurrently. We followed infants for 30 days after each dose for diagnoses of intussusception, other gastrointestinal events, seizures, Kawasaki disease, thrombocytopenia, otitis media, all-cause emergency department visits, and all-cause hospitalizations. We estimated adjusted hazard ratios (HR) and 95% confidence intervals (CI) with multivariable Cox proportional hazards models comparing: (i) those receiving DTaP+RV versus those receiving DTaP alone; and (ii) RV5 versus RV1. Analyses were performed separately within DTaP doses and then meta-analysed across doses.

Results—We identified 1,031,431 first DTaP doses, 821,833 second doses, and 615,293 third doses; 79.2% had a concurrent RV, 94.1% of which were RV5. Absolute risks of serious outcomes were very low. Compared to infants who received DTaP alone, infants who received RV+DTaP did not experience consistently increased risk of intussusception (hazard ratio [HR] 1.13, 95% confidence interval [CI] 0.68–1.88) or any other outcome except for otitis media after dose 2: HR

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1.11, 95% CI 1.08-1.15. This increased otitis media risk was not as pronounced in RV5 when comparing RV5 to RV1; HR 0.92, 95% CI 0.89-0.95.

Conclusions—These data were not consistent with an increased risk of intussusception or other adverse events following vaccination with RV, except potentially for a small increased risk of otitis media, particularly in RV1.

Keywords

Immunization; intussusception; safety; administrative claims; epidemiology

Background

The use of rotavirus vaccine (RV) has become widespread in the United States, leading to substantial reduction in diarrheal illness among young children. Prior to the availability of RV, rotavirus infection resulted in hundreds of thousands of office and emergency department visits in children less than 5 years of age in the U.S.^{1, 2} There are two currently-used live, oral RVs approved and recommended for routine use among U.S. infants: 3-dose pentavalent (RV5) approved in February 2006, and 2-dose monovalent (RV1) approved in April 2008.² Recent observational studies have suggested that RV has dramatically reduced hospitalizations among young children³; however, RV remains underutilized,^{4, 5} and concerns about the safety of the vaccines persist.

The first RV formulation was withdrawn in 1999 due to its association with intussusception,⁶ an acute and serious enfolding of the intestine which can result in bowel obstruction or loss of blood supply to the intestine. Although large pre-licensure clinical trials of the new RV5 and RV1 ruled out intussusception risks equal to that of the previous RV, a post-market case-control study found increased risks of intussusception in Brazilian and Mexican infants vaccinated with RV1, and a post-market cohort study of Australian infants found increased risks of intussusception following vaccination with RV1 and RV5 compared to unvaccinated infants.⁷⁻⁹ However, studies demonstrating the increased risk of RV-associated intussusception have been inconsistent across different populations. In 3 large studies of US children, one RV1 showed an increased risk compared to historical background rates,¹⁰ another showed no increase for RV5 compared to unvaccinated children,¹¹ and another did show increases with RV5 but inconclusive results about RV1.¹² Additionally, natural rates of intussusception vary widely between countries, sexes, and age groups.¹³⁻¹⁹

In addition to intussusception, some case reports suggest that natural rotavirus infection may be associated with conditions such as encephalitis and seizures,²⁰⁻²² which raises safety concerns for live rotavirus vaccinations. However, these hypothesized adverse events have not been observed in connection with RV in large, population studies. Given concerns about RV-induced intussusception, the recommended RV administration during the peak ages of natural intussusception incidence, and the scarce safety data directly comparing RV5 to RV1 in U.S. infants for other safety outcomes, we sought to analyze a large cohort of U.S. infants using carefully developed methods to evaluate the safety of RV, overall and by vaccine formulation.

Methods

Data Source and Population

We identified newborns at birth in the MarketScan Commercial Claims and Encounters database (Copyright © 2016 Truven Health Analytics Inc., All Rights Reserved.) during the years 2006-2014. These administrative databases contain insurance billing claims and enrollment information for employees, spouses, and dependents from over 100 employer-sponsored insurance plans from throughout the United States.

Newborns were identified with International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes for live birth (V30-V39). The date of occurrence of the first code per child was considered the date of delivery. We excluded babies born in states with state-provided vaccines (Alaska, Idaho, Massachusetts, Maine, North Dakota, New Hampshire, New Mexico, Oregon, Rhode Island, Vermont, Washington, Wisconsin, Wyoming) as we would have been unable to observe individual-level vaccine billing claims in these states.²³ We required continuous health plan enrollment from birth until the vaccination event, although we allowed a 7-day post-birth grace period for the beginning of continuous coverage to allow for initial plan enrollment.

Exposure Assessment

We anchored all our RV assessments and analyses on the receipt of a diphtheria-tetanus-pertussis (DTaP) vaccine dose; newborns were followed from the date of birth to one year of age to observe DTaP doses and determine if RV was administered on the same day. Infant DTaP coverage is very high in the US,²⁴ and DTaP and RV are frequently received together in the same visit; RV and DTaP follow similar dosing schedules, with recommended doses at 2, 4, and 6 months (except for the 2-dose RV1 which does not have a 6-month dose) with doses at least 4 weeks apart. We identified infants who received at least one dose of DTaP vaccine, and we included up to 3 DTaP doses per infant in the study, creating a separate record for each dose (Figure 1). We identified the receipt of DTaP vaccines in insurance claims using Current Procedure Terminology (CPT) codes for DTaP administration (90696, 90698, 90700, 90701, 90711, 90715, 90720, 90721, 90723).

We identified RV administration occurring on the same day as DTaP with CPT codes (90680, RV5; 90681, RV1). We categorized each DTaP dose as concurrently vaccinated with either RV5 or RV1, or DTaP received alone. Each dose was considered independently; an infant's RV status could vary across DTaP doses, allowing for mixed series of RV1 and RV5, incomplete RV series, and delayed RV doses (e.g. the first RV dose received at the second DTaP vaccination).

Outcome Assessment

We defined study outcomes using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes and procedure coding for events occurring on the day of and in the 30 days after vaccination. Intussusception was identified through an inpatient diagnosis code for intussusception or a procedure code for a therapeutic enema to correct intussusception.²⁵

Other events identified during 30 days post-vaccination included: gastrointestinal events, including diarrhea, blood in stool, and appendicitis; Kawasaki disease; neurological events, including seizure, meningitis, encephalitis, and febrile convulsions; thrombocytopenia; otitis media; all-cause hospitalization; and all-cause emergency room visits (Supplementary Table 1). We also identified events occurring in the 30 days prior to vaccination, allowing us to exclude those with pre-existing disease, ensuring identification of new-onset outcomes post-vaccination.

Previous research has suggested an increased risk of intussusception in the 7-days post-vaccination;^{10, 26} additionally, some study outcomes are relatively common in early childhood, and events 30 days after vaccination may be less-likely to be attributable to the vaccination. Therefore, we performed a sensitivity analysis using a shorter, 7-day follow-up period rather than the full 30-days for some outcomes, including intussusception, seizures, diarrhea, blood in stool otitis media, all-cause emergency department visits, and all-cause hospitalization.

Covariate Assessment

We assessed infant characteristics to account for potential differences between treatment groups, including sex, age at dose receipt, geographic region, and year. As many vaccinations can be received at the same visit, and several other vaccines are indicated in infants of the same age, we also assessed concurrent vaccination with the following: hepatitis B, Haemophilus influenzae type B, polio, pneumococcal, and influenza.

Statistical Analysis

Infants were followed post-vaccination for up to 30 days, with censoring occurring at the earliest of: 30 days post-vaccination, disenrollment from the health plan, end of study, or receipt of a subsequent RV dose. To evaluate the safety of RV receipt, we compared adverse event rates following RV and DTaP received on the same day (RV+DTaP) to event rates after doses of DTaP without concurrent RV. We utilized DTaP received alone as a comparator group and did not include RV doses received without a concurrent DTaP dose to lessen potential unmeasured confounding introduced by differing access to healthcare, health behaviors and beliefs, and other important differences between vaccine receivers and non-receivers. Also, comparing RV+DTaP to DTaP alone allowed us to reduce potential surveillance bias by aligning outcome ascertainment windows after routine infant healthcare encounters indicated by the DTaP dose, and to better isolate the effect of RV, as many vaccines can be received at one time.

We compared the rates of adverse events in infants receiving RV+DTaP versus DTaP alone using Cox proportional hazards models, estimating hazard ratios (HR) and 95% confidence intervals (CI). As each infant could receive multiple doses at different ages, and outcome incidences and confounding factors can vary widely by age during the first few months of life, we stratified the analysis by DTaP dose (e.g., RV+DTaP dose 1 vs. DTaP alone dose 1; RV+DTaP dose 2 vs. DTaP alone dose 2; RV+DTaP dose 3 vs. DTaP alone dose 3) to report dose-specific estimates, and then pooled estimates across doses using fixed-effect meta-

analysis models to obtain overall estimates. Infants could be included in the separate analyses of all 3 doses.

Individual doses were excluded if the child was diagnosed with intussusception at any time prior to the dose, as prior intussusception is a contraindication for RV receipt. For each outcome-specific analysis, we excluded infants who had any diagnosis of the outcome of interest in the 30-days prior to vaccination to capture incident episodes of the outcome events. The models were adjusted for infant's sex, birth year, age in weeks at vaccination (categorized as 0-9, 10-19, 20-29, 30-39, 40-49, 50-52 weeks), US geographic region, and concurrent vaccination receipt (hepatitis B, Haemophilus influenzae type B, Pneumococcal, polio, influenza).

Additionally, we assessed safety differences by RV formulation, comparing RV5+DTaP to RV1+DTaP within doses 1 and 2. For the comparison of dose 2, we required the RV formulation to be the same for dose 1 and dose 2 (e.g. a non-mixed series of either RV1 or RV5). As RV1 is a 2-dose series, we did not perform a dose 3 comparison.

The analysis was approved by the institutional review board of the University of North Carolina at Chapel Hill. Individual consent was not required for this secondary analysis of deidentified data. Analyses were performed with SAS 9.4 (SAS Institute, Cary, NC).

Results

We identified 1,031,431 infants receiving at least one dose of DTaP (51.6% male; mean age at first DTaP dose=11.2 weeks, SD 5.0); we observed a second dose for 821,833 (79.7%) infants (mean age=19.7 weeks, 4.2 SD), and a third dose for 615,293 (59.7%) infants (mean age=28.0 weeks, SD 3.4). The majority of infants received RV concurrently with DTaP, including 80.8% of infants for dose 1, 80.7% of infants for dose 2, and 74.5% of infants for dose 3. Of all the concurrent RV doses, 94.1% were RV5. Concurrent RV receipt increased over the study period, from 37.0% in 2006 to 90.5% in 2014. (Table 1; Supplementary Table 2). There were differences in geographic distributions between the RV receivers and non-receivers, with RV being more common in the South and less common in the Northeast. The RV1 and RV5 receivers were very similar in terms of sex, age, and US region, although RV1 was introduced later in the study period. Co-administration of other vaccines varied between the RV+DTaP and the DTaP alone groups, both within a dose (Table 1) and across doses (Supplementary Table 2).

The incidence of post-vaccination outcomes varied widely. The most common outcomes included otitis media (4.2%) and emergency department visits (2.6%). Serious events were extremely rare, with very small case counts (Tables 2–3). Infant follow-up was censored during the 30-day follow-up window after 5.4% of doses; 0.9% censoring events were due to a subsequent RV dose within 30 days, and the remainder were administratively censored due to plan disenrollment or end of study period.

Across all doses of RV, intussusception was rare, with 28 cases occurring within 7 days and 108 within 30 days following 2,468,011 RV doses. 30-day intussusception rates were lower following the first RV dose (34 cases; 4.1 cases/100,000 doses) than after dose 2 (46 cases;

6.9 cases/100,000 doses) or dose 3 (28 cases; 6.1 cases/100,000 doses), consistent with the established understanding that natural intussusception risk increases over the first six months of an infant's life.^{18, 27}

When comparing any RV+DTaP to DTaP alone, we did not observe consistently increased intussusception rates associated with RV; the HRs were slightly elevated though imprecise (pooled HR=1.13 [95% CI: 0.68, 1.88]). The effect estimates for dose 2 (HR=2.32 [95% CI: 0.90, 5.96]) were higher than other dose estimates, though the relative imprecision of the estimates resulted in statistically consistent effect measure estimates across doses (p for homogeneity=0.16) (Table 2). We did not observe differential 30-day intussusception risk in RV5 vs. RV1 (pooled HR=1.02 [95% CI: 0.42, 2.60], p for homogeneity=0.61) (Table 3).

The post hoc intussusception analysis considering only 7 days of follow-up rather than 30 was limited by small numbers, with only 3 intussusception cases within 7 days of the 513,087 DTaP alone doses. Similar to the 30-day analysis, the pooled HR was elevated, though imprecise, HR=1.71 [95% CI: 0.43, 6.88], with the dose 2 estimate being the most elevated, (HR=1.84 [95% CI: 0.32, 10.62]), though imprecision around all estimates resulted in p for homogeneity=0.90. Case counts were too low to estimate RV5 vs. RV1 comparisons with 7 days (Supplementary Table 3).

We did not observe consistently elevated rates of other outcomes associated with RV (Table 2), except for small, potentially elevated rates of otitis media, although the relative increases were quite small—pooled HR=1.04 [95% CI: 1.02, 1.06]—but the associations varied by dose (p for homogeneity<0.001), with essentially null associations with dose 1 and 3, but an elevated association observed after dose 2, HR=1.11 [95% CI: 1.08, 1.15]. This association was less pronounced in RV5 compared to RV1, with a pooled HR of 0.92 [95% CI: 0.89, 0.95] and was consistent across doses 1 and 2 (p for homogeneity=0.53) (Table 3).

Otitis media incidence varies by several factors, including sex²⁸ and geography; additionally, otitis media incidence decreased after the March 2010 introduction of the pneumococcal conjugate vaccine.²⁸ However, in post hoc subgroup analyses, the observed otitis media association with RV dose 2, and specifically with RV1, was consistent across levels of sex, US region, and time period (Supplementary Table 4).

Overall, RV was associated with some reduced rates of certain outcomes: encephalitis (pooled HR=0.53 [95% CI: 0.29, 0.97]; p for homogeneity=0.91), seizure (pooled HR=0.85 [95% CI: 0.72, 0.99]; p for homogeneity=0.05), all-cause emergency room visits (pooled HR=0.91 [95% CI: 0.89, 0.92]; p for homogeneity=0.43); and all-cause hospitalization (HR=0.83 [95% CI: 0.78, 0.87]; p for homogeneity=0.12). We did not observe differential risk by vaccine formulation for any other outcomes. The post hoc 7-day follow-up analyses were quite consistent with the 30-day results for all considered outcomes (Supplementary Table 3).

Comment

Principal findings

In this large study of US infants receiving DTaP with or without RV, we did not observe a consistently increased risk of intussusception associated with RV in the 30 days post-vaccination for either vaccine formulation, and overall, the number of cases and rates were very low. Rates of intussusception varied with age, and the estimates were consistent with a null finding across the 3 doses, generally given at 2, 4, and 6 months of age; however, the 30-day HR at dose 2 was higher than the other doses, but the small number of cases and imprecision around the estimate resulted in similar, null conclusions. While these data don't indicate evidence of increased intussusception risks overall equal to previously-published studies, the dose 2 estimate may be consistent with a small increase observed in previous studies in various populations.

Strengths of the study

In our cohort study, we restricted to infants who received DTaP immunization in our study, attempting to create a more homogenous group of vaccine recipients to reduce confounding bias by healthcare-seeking behavior, adherence to recommendations, access to preventive care, attitudes, and beliefs, all of which are difficult to measure independently in insurance claims. Additionally, by comparing within strata of DTaP doses, we were able to align RV and non-RV receivers at equivalent points in their age and healthcare-seeking behaviors, accounting for changing outcome risks and healthcare observation across infancy. While RV is not recommended in infants over 8 months (approximately 35 weeks), we included all doses given throughout the first year of life, as there were a substantial number of RV doses received after 35 weeks. While RV5 was much more common than RV1, the characteristics of the groups were similar, suggesting that the potential confounding between the two groups was minimal.

This large, administrative claims-based cohort contained newborns from across the US being evaluated and cared for in a variety of healthcare settings; however, if a vaccine was received and paid for out-of-pocket or the claim not submitted to the insurer, we would not observe the vaccination event. However, by restricting to DTaP receivers, we assumed we were more likely to observe RV vaccination claims, and RV vaccines have been shown to be only infrequently misclassified using claims.²⁹

Limitations of the data

Since insurance billings claims represent the basis for payment and not detailed clinical records, we were unable to measure the severity of intussusception or other outcomes, and some outcomes may be misclassified due to coding errors. Additionally, our sample is limited to those with employer-based insurance and may not be generalizable to those with Medicaid, the uninsured, or non-US children. As natural intussusception rates and rotavirus infection rates can differ widely in different countries, climates, and populations, continued investigation in diverse settings is needed.

By restricting our analysis to those receiving DTaP, the generalizability of the study may be limited to only children receiving DTaP; however, DTaP coverage is extremely high, and this restriction anchors RV receivers and non-receivers at equivalent points in their clinical experience, implicitly controlling for several important potential confounders such as vaccine-avoiding behavior and attitudes, access to healthcare, current health status, and vaccine schedule-keeping behavior—major confounders of studies comparing vaccine receivers to non-receivers. However, by requiring DTaP co-administration, we would be unable to disentangle any synergistic effects or interactions of RV and DTaP administered together. Additionally, unmeasured confounding may remain which was not accounted for by the study design or adjustment variables, and even after anchoring RV receivers and non-receivers on DTaP receipt, the mean age at RV+DTaP doses tended to be slightly younger than at doses of DTaP received alone. Vaccine co-administration varied between RV and non-RV groups; this may be partially explainable by time trends of RV introduction and (e.g. PCV and RV, particularly RV1, were more common later in the study period) or schedules (e.g. influenza vaccine is indicated in infants 6+ months, generally overlapping with RV5's 3rd dose but not earlier doses), but there remains a wide range of vaccine uptake not always aligned with recommendations.

While the use of large insurance data allows for a large study population of children throughout the US treated in a variety of settings, our case counts of intussusception and some other rare outcomes were quite small—particularly in the 7-day analyses—occasionally making direct comparisons between treatment groups difficult. Our observed intussusception rate was less than that observed in other studies¹⁸; medical chart validation of exposures and outcomes was not possible due to the deidentified nature of the data source, and we may have missed some true outcome cases if the insurance billing claim was incomplete or incorrectly coded. While any potential misclassification of study outcomes was unlikely to be differential between RV5 and RV1 recipients, differential misclassification of intussusception may have occurred between the RV+DTaP and DTaP-only groups if providers scrutinized infants who received concurrent RV more closely than those who received only DTaP due to fear of intussusception; since this effect would bias the HRs presented in this study away from the null, any impact of this differential misclassification would not change the conclusions presented in this study.

Interpretation

The results from our cohort study differ somewhat from the generally increased intussusception risks reported in previous self-controlled studies^{12, 30} which may be confounded by the changing within-person risk of intussusception during infancy, and user vs. non-user cohort designs may be confounded by differences between vaccine receivers and non-receivers.

We observed a small increased risk of otitis media associated with RV dose 2 in both 7-day and 30-day analysis. Otitis media has previously been reported as potentially being associated with rotavirus infection in small studies^{31, 32} as rotavirus can colonize the upper respiratory tract, including the inner ear; additionally, otitis media had been observed as an unsolicited adverse event in RV trials.³³ While we describe a relative increase in otitis media

risk associated with RV dose 2, the magnitude of the effect was quite small and was not consistent across all doses. Otitis media was quite common in the infants and is generally considered a non-serious event. Additionally, an increased association of RV with meningitis was observed after dose 2; this association was not consistent across doses and was based on very small sample sizes (with only 2 cases in the DTaP alone group), resulting in substantial imprecision of the estimate and very wide confidence intervals.

We did observe some small protective associations for some outcomes: it was not our a priori intention to evaluate protective effects, so we choose to not emphasize them, yet the slight reduction in seizures we observed is consistent with previous research.^{34, 35} While the 30-day post-vaccination follow-up is short, the reductions in hospitalizations and emergency department visits may be due to the effectiveness of the vaccine in preventing rotavirus-associated illness.

Conclusions

Overall, we did not demonstrate an association between RV and serious adverse events, and the safety was comparable between the two RV formulations, though many events were rare. RV may be associated with a small increased risk of otitis media, but further research is necessary to confirm this association.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Study design schematic of pre- and post-vaccination observation periods for diphtheria-tetanus-pertussis (DTaP) doses and concurrent rotavirus vaccination (RV) of a hypothetical infant from birth to one year

Table 1

Characteristics of diphtheria-tetanus-pertussis (DTaP) vaccine receivers by concurrent rotavirus vaccine (RV) receipt at the first dose received

Characteristic	Overall n (%)	DTaP alone n (%)	All RV+DTaP n (%)	RV1+DTaP* n (%)	RV5+DTaP* n (%)
Total infants	1,031,431	197,774	833,657	66,662	766,856
Female Sex, No. (%)	499,750 (48.5)	95,106 (48.1)	404,644 (48.5)	32,583 (48.9)	371,997 (48.5)
Age (weeks, mean [SD])	11.2 (5.0)	13.4 (7.5)	10.7 (4.1)	11.1 (4.2)	10.6 (4.1)
Year of birth, No. (%)					
2006	53,783 (5.2)	33,863 (17.1)	19,920 (2.4)	0 (0.0)	19,920 (2.6)
2007	79,976 (7.8)	26,900 (13.6)	53,076 (6.4)	1 (0.0)	53,074 (6.9)
2008	109,974 (10.7)	28,512 (14.4)	81,462 (9.8)	1,876 (2.8)	79,574 (10.4)
2009	123,115 (11.9)	22,860 (11.6)	100,255 (12.0)	11,833 (17.8)	88,395 (11.5)
2010	138,591 (13.4)	22,534 (11.4)	116,057 (13.9)	10,830 (16.3)	105,191 (13.7)
2011	161,540 (15.7)	21,592 (10.9)	139,948 (16.8)	15,760 (23.6)	124,163 (16.2)
2012	150,730 (14.6)	17,886 (9.0)	132,844 (15.9)	11,742 (17.6)	121,081 (15.8)
2013	113,089 (11.0)	14,057 (7.1)	99,032 (11.9)	8,118 (12.2)	90,906 (11.9)
2014	100,633 (9.8)	9,570 (4.8)	91,063 (10.9)	6,502 (9.8)	84,552 (11.0)
US region, No. (%)					
Northeast	177,210 (17.2)	45,632 (23.1)	131,578 (15.8)	10,897 (16.4)	120,662 (15.7)
North Central	308,041 (29.9)	87,077 (28.9)	250,964 (30.1)	18,986 (28.5)	231,950 (30.3)
South	426,589 (41.4)	71,417 (36.1)	355,172 (42.6)	30,484 (45.7)	324,605 (42.3)
West	105,791 (10.3)	20,863 (10.6)	84,928 (10.2)	4,846 (7.3)	80,074 (10.4)
Unknown	13,800 (1.3)	2,785 (1.4)	11,015 (1.3)	1,449 (2.2)	9,565 (1.3)
Concurrently received vaccinations, No. (%)					
Hepatitis B	422,870 (41.0)	50,243 (25.4)	372,627 (22.7)	34,903 (52.4)	337,651 (44.0)
Haemophilus influenzae type B	309,169 (30.0)	90,667 (45.8)	218,502 (26.2)	8,726 (13.1)	209,727 (27.4)
Polio	942,202 (91.4)	155,219 (78.5)	786,983 (94.4)	62,894 (94.4)	723,958 (94.4)
Pneumococcal	919,354 (89.1)	133,705 (67.6)	785,649 (94.2)	62,239 (93.3)	723,285 (94.3)
Influenza	8,950 (0.9)	3,338 (1.7)	5,612 (0.7)	153 (0.2)	5,458 (0.7)

DTaP, diphtheria-tetanus-pertussis vaccine; RV1, 2-dose monovalent rotavirus vaccine; RV5, 3-dose pentavalent rotavirus vaccine; RV+DTaP, RV and DTaP concurrently received on the same day; SD, standard deviation

* RV1 and RV5 subsets do not sum to the Any RV group due to the exclusion of RV recipients receiving different formulations for the first and second doses

Table 2
Association of adverse events with any rotavirus vaccination (RV) with concurrent diphtheria-tetanus-pertussis (DTaP) versus DTaP alone

Outcome	Dose	Total number	Number of cases	Hazard ratio (95% confidence interval)	
				Unadjusted	Adjusted
Intussusception	1	1,031,314	42	0.99 (0.46, 2.14)	0.84 (0.35, 2.03)
	2	821,642	53	1.55 (0.70, 3.43)	2.32 (0.90, 5.96)
	3	615,073	36	1.19 (0.54, 2.62)	0.83 (0.36, 1.93)
	Pooled				1.13 (0.68, 1.88)
Kawasaki Disease	1	1,031,308	1	--	--
	2	821,621	13	0.53 (0.16, 1.72)	0.54 (0.14, 2.07)
	3	615,060	9	0.68 (0.17, 2.73)	0.55 (0.12, 2.48)
	Pooled				0.54 (0.20, 1.48)
Seizure	1	1,030,651	498	0.78 (0.63, 0.95)	0.83 (0.65, 1.07)
	2	821,315	346	0.95 (0.73, 1.23)	1.14 (0.84, 1.56)
	3	614,882	267	0.58 (0.45, 0.74)	0.68 (0.51, 0.90)
	Pooled				0.85 (0.72, 0.99)
Meningitis	1	1,030,787	97	1.18 (0.69, 2.01)	1.26 (0.69, 2.33)
	2	821,581	31	3.42 (0.82, 14.34)	5.13 (1.13, 23.26)
	3	615,051	13	1.88 (0.42, 8.46)	1.35 (0.28, 6.53)
	Pooled				1.52 (0.89, 2.59)
Encephalitis	1	1,031,240	29	0.44 (0.21, 0.95)	0.47 (0.19, 1.16)
	2	821,621	23	0.44 (0.19, 1.04)	0.63 (0.23, 1.72)
	3	615,069	10	0.34 (0.10, 1.18)	0.50 (0.12, 2.15)
	Pooled				0.53 (0.29, 0.97)
Diarrhea	1	1,023,734	7,491	0.92 (0.87, 0.98)	0.94 (0.87, 1.00)
	2	814,602	6,627	0.98 (0.92, 1.04)	0.96 (0.90, 1.03)
	3	609,558	5,012	0.92 (0.87, 0.98)	0.93 (0.87, 1.00)
	Pooled				0.94 (0.91, 0.98)
Blood in Stool	1	1,026,924	2,803	1.23 (1.12, 1.37)	1.07 (0.95, 1.20)
	2	819,755	1,416	1.20 (1.04, 1.38)	--
	3	614,208	512	1.15 (0.94, 1.42)	0.93 (0.79, 1.09)

Outcome	Dose	Total number	Number of cases	Hazard ratio (95% confidence interval)	
				Unadjusted	Adjusted
Appendicitis	Pooled				1.00 (0.79, 1.25)
	1	1,031,302	5	--	--
	2	821,638	5	0.35 (0.06, 2.11)	0.40 (0.05, 3.01)
Febrile Convulsions	3	615,071	0	--	--
	Pooled				--
	1	1,031,238	72	0.57 (0.34, 0.94)	1.22 (0.62, 2.38)
Thrombocytopenia	2	821,592	88	0.99 (0.58, 1.67)	1.36 (0.75, 2.49)
	3	614,996	122	0.44 (0.31, 0.64)	0.67 (0.43, 1.02)
	Pooled				0.91 (0.67, 1.24)
Otitis Media	1	1,030,809	108	0.70 (0.45, 1.09)	0.66 (0.40, 1.10)
	2	821,546	55	1.06 (0.54, 2.11)	1.44 (0.66, 3.15)
	3	615,030	50	0.88 (0.47, 1.63)	0.97 (0.48, 1.96)
All-cause ED visit	Pooled				0.87 (0.60, 1.25)
	1	1,015,602	20,567	0.75 (0.72, 0.77)	1.02 (0.99, 1.06)
	2	787,887	36,747	0.95 (0.93, 0.98)	1.11 (1.08, 1.15)
All-cause hospitalization	3	565,720	41,847	0.97 (0.95, 0.99)	1.00 (0.98, 1.03)
	Pooled				1.04 (1.02, 1.06)*
	1	995,933	24,739	0.83 (0.81, 0.86)	0.90 (0.86, 0.93)
	2	800,889	19,847	0.82 (0.79, 0.84)	0.89 (0.86, 0.93)
	3	598,604	16,953	0.89 (0.86, 0.92)	0.92 (0.88, 0.95)
	Pooled				0.91 (0.89, 0.92)
	1	1,010,160	4,973	0.74 (0.69, 0.79)	0.79 (0.73, 0.85)
	2	817,450	2,800	0.75 (0.69, 0.82)	0.83 (0.75, 0.92)
	3	612,879	1,692	0.84 (0.75, 0.93)	0.91 (0.81, 1.02)
	Pooled				0.83 (0.78, 0.87)

ED, emergency department

Multivariable models adjusted for: child's age (categorized in 10-week increments), year of vaccine administration, sex, US region, and concurrent vaccination receipt (hepatitis B, Haemophilus influenzae type B, Pneumococcal, polio, influenza).

* P for homogeneity < 0.05

-- denotes too few cases for models to converge

Table 3

Association of adverse events with pentavalent rotavirus vaccination (RV5) with concurrent diphtheria-tetanus-pertussis (DTaP) versus monovalent rotavirus vaccination (RV1) with concurrent DTaP

Outcome	Dose	Total Number	Number of cases	Hazard ratio (95% confidence interval)	
				Unadjusted	Adjusted
Intussusception	1	833,439	34	1.39 (0.33, 5.79)	1.39 (0.33, 5.86)
	2	635,037	44	0.88 (0.27, 2.85)	0.85 (0.26, 2.80)
Kawasaki Disease	Pooled				1.04 (0.42, 2.60)
	1	833,434	1	--	--
	2	635,026	8	--	--
	Pooled				--
Seizure	1	832,957	383	1.02 (0.70, 1.48)	1.04 (0.71, 1.52)
	2	634,808	263	0.74 (0.48, 1.16)	0.80 (0.51, 1.25)
Meningitis	Pooled				0.93 (0.70, 1.24)
	1	833,011	81	0.79 (0.38, 1.65)	0.76 (0.36, 1.60)
	2	634,992	27	0.52 (0.16, 1.72)	0.48 (0.14, 1.65)
	Pooled				0.67 (0.36, 1.27)
Encephalitis	1	833,388	19	--	--
	2	635,024	14	0.84 (0.11, 6.42)	0.74 (0.09, 5.76)
Diarrhea	Pooled				--
	1	827,476	5,986	0.99 (0.90, 1.08)	0.99 (0.90, 1.08)
	2	629,680	5,084	0.99 (0.90, 1.13)	1.05 (0.93, 1.18)
	Pooled				1.01 (0.94, 1.08)
Blood in Stool	1	829,896	2,357	1.14 (0.97, 1.36)	1.11 (0.95, 1.30)
	2	633,611	1,116	1.10 (0.85, 1.42)	1.17 (0.91, 1.52)
Appendicitis	Pooled				1.13 (0.98, 1.29)
	1	833,428	5	--	--
	2	635,033	3	--	--
	Pooled				--
Febrile Convulsions	1	833,388	51	1.39 (0.43, 4.46)	1.20 (0.37, 3.92)
	2	634,981	68	0.81 (0.33, 2.02)	0.84 (0.33, 2.11)

Outcome	Dose	Total Number	Number of cases	Hazard ratio (95% confidence interval)	
				Unadjusted	Adjusted
Thrombocytopenia	Pooled				0.96 (0.47, 1.99)
	1	833,068	81	1.32 (0.53, 3.26)	1.24 (0.50, 3.10)
	2	634,971	42	0.84 (0.26, 2.72)	0.85 (0.26, 2.80)
Otitis Media	Pooled				1.08 (0.52, 2.23)
	1	821,929	15,729	0.91 (0.86, 0.96)	0.91 (0.86, 0.96)
	2	609,818	28,250	0.98 (0.93, 1.02)	0.93 (0.88, 0.97)
All-cause ED visit	Pooled				0.92 (0.89, 0.95)
	1	805,902	19,364	1.00 (0.95, 1.05)	1.00 (0.95, 1.05)
	2	619,781	14,600	0.98 (0.92, 1.05)	0.95 (0.89, 1.02)
All-cause hospitalization	Pooled				0.98 (0.94, 1.02)
	1	817,368	3,787	0.98 (0.87, 1.10)	0.94 (0.84, 1.06)
	2	632,114	2,015	0.98 (0.82, 1.17)	0.98 (0.81, 1.17)
ED, emergency department	Pooled				0.95 (0.86, 1.05)

ED, emergency department

Multivariable models adjusted for: child's age (categorized in 10-week increments), year of vaccine administration, sex, US region, and concurrent vaccination receipt (hepatitis B, Haemophilus influenzae type B, Pneumococcal, polio, influenza).

-- denotes too few cases for models to converge