ROTAVIRUS VACCINE COMPLIANCE AND COMPLETION AMONG INFANTS IN MANAGED CARE

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BACKGROUND

Rotavirus causes gastroenteritis and diarrhea, especially in young children, and, although mortality due to infection is low in the United States, diarrhea and associated dehydration are still of concern. Two rotavirus vaccines are currently approved for use in the United States: three-dose RotaTeq (RV5; Merck & Co., Inc., Whitehouse Station, New Jersey) is administered at ages 2, 4, and 6 months; and two-dose Rotarix (RV1; GlaxoSmithKline, Research Triangle Park, North Carolina) is administered at ages 2 and 4 months.

OBJECTIVE

To compare rotavirus vaccine series completion and dosing schedule compliance among infants who receive the two-dose vaccine with those who receive the three-dose vaccine.

METHODS

Study population

- Infants aged less than 1 year who initiated a rotavirus vaccine in the period from 01 January 2009 through 30 June 2009 and were continuously enrolled in their health plan through age 9 months were identified using US health insurance claims data.
  - Infants were required to have data available regarding sex, region, and birth date. They must have been enrolled in the health plan within 1 month of birth and continuously enrolled between enrollment and index rotavirus vaccination.
  - The date of the first rotavirus vaccination during 01 January 2009 through 30 June 2009 was defined as the index date.
- Rotavirus vaccine brand and dates of administration were determined based on claims with CPT codes 90680 (RV5) or 90681 (RV1).
- Two cohorts were formed based on receipt of the same brand (RV5 or RV1) for all doses. Infants who received a mixed series were excluded from the analyses.
- Infants were observed until the earliest of: disenrollment from the health plan, age 1 year, or 31 March 2010.
- Privacy board approval was obtained in order to link subject birth dates to the claims data. All other data were de-identified. Pursuant to the Health Insurance Portability and Accountability Act, the use of de-identified data does not require Institutional Review Board approval or waiver of authorization.

Completion and compliance

- Series completion required evidence of receipt of a full valid vaccine series prior to age 1 year: three valid doses for those in the RV5 cohort and two valid doses for infants in the RV1 cohort. "Valid" doses (Table 1) meet general immunization guidelines for vaccine dose spacing as defined by the ACIP.[1] If a vaccination occurred prior to the minimum age, it was considered invalid and an interval of at least 4 weeks was required before the following vaccination could be considered an on-schedule Dose 1 according to valid or harmonized schedules.
- Missed doses and dose timing were both considered in the assessment of compliance. Schedule compliance was determined by comparing the timing of doses administered against the brand-specific FDA-approved dosing schedules and the harmonized ACIP rotavirus vaccine schedule (Table 1).
- Infants aged less than 1 year who initiated a rotavirus vaccine in the period from 01 January 2009 through 30 June 2009 and were continuously enrolled in their health plan through age 9 months were identified using US health insurance claims data.

Statistical analysis

- The proportions of infants that completed their vaccine series and complied with FDA-approved or harmonized dosing schedules are reported. Logistic regression models were used to assess differences in completion and compliance by vaccine brand while adjusting for sex, index month, geographic region, and immunization provider type.
- Data extraction and statistical analyses were performed using SAS, version 9.1.3 (SAS Institute, Cary, NC).

Table 1. Rotavirus Vaccine Dose Administration Schedules

		Series Completion	Dose Compliance		
Vaccine Dose		Valid Immunization[1]	ACIP Harmonized Rotavirus Vaccination Schedule[2]	FDA-approved RV5 Schedule[3]	FDA-approved RV1 Schedule[4]
Minimum age for first dose		6 weeks (-4 days[a])	6 weeks	6 weeks	6 weeks
Maximum age for any dose		NA	8 months and 0 days	32 weeks	24 weeks
Dose 1	Schedule	Age 6 weeks (-4 days[a]) and older	Age 6 weeks through 2 months	Age 6 weeks through 12 weeks	Age 6 weeks
	Study definition	Age ≥38 days	Age 42-91 days	Age 42-84 days	Age 42-140 days
Dose 2	Schedule	At least 4 weeks (-4 days[a]) after previous dose	Age 4 months and ≥4 weeks after the previous dose	4-10 weeks after the previous dose	≥4 weeks after the previous dose
	Study definition	≥24 days after the previous dose	Age ≤152 days and ≥28 days after the previous dose	Age ≤224 days and 28-70 days after the previous dose	Age ≤168 days and 28-70 days after the previous dose
Dose 3	Schedule	At least 4 weeks (-4 days[a]) after previous dose	Age 6 months and ≥4 weeks after the previous dose	4-10 weeks after the previous dose	–
	Study definition	≥24 days after the previous dose	Age ≤214 days and ≥28 days after the previous dose	Age ≤224 days and 28-70 days after the previous dose	

[a]Doses administered up to 4 days prior to the minimum acceptable age are considered valid.
ACIP, Advisory Committee on Immunization Practices; FDA, Food and Drug Administration; NA, not applicable.

RESULTS

Characteristics of the study sample are shown in **Table 2**.

Table 2. Study Sample Characteristics

Characteristic	Total (N=55,584)	RV1 (N=6130)	RV5 (N=49,454)	P[a]
Sex; n (%)				
Male	28,426 (51.1)	3162 (51.6)	25,264 (51.1)	0.463
Female	27,158 (48.9)	2968 (48.4)	24,190 (48.9)	
Immunization provider; n (%[b])				
Pediatrician	51,140 (92.0)	5746 (93.7)	45,394 (91.8)	<0.001
Family practice	3960 (7.1)	306 (5.0)	3654 (7.4)	<0.001
Other	406 (0.7)	69 (1.1)	337 (0.7)	<0.001
Unknown	78 (0.1)	9 (0.2)	69 (0.1)	0.886
Geographic region; n (%[b])				
Northeast	6554 (11.8)	899 (14.7)	5655 (11.4)	<0.001
Midwest	14,834 (26.7)	1879 (30.7)	12,955 (26.2)	<0.001
South	24,573 (44.2)	2619 (42.7)	21,954 (44.4)	0.013
West	9623 (17.3)	733 (12.0)	8890 (18.0)	<0.001

[a]Chi-square test.
[b]Might not sum to 100% due to rounding.

Completion

- Overall, 84.3% of infants in the study cohorts completed a full vaccine series (Table 3).
- After adjustment, odds of series completion for infants in the RV1 cohort were approximately double the odds for the RV5 cohort (odds ratio [OR] 1.9; 95%CI 1.8-2.1; *P*<0.001).
- Mean (±SD) age at series completion was approximately 4 months (130.2±17.1 days) for RV1 and approximately 6 months (191.3±14.5 days) for RV5 (*P*<0.001).

Table 3. Rotavirus Vaccine Series Completion

	Total (N=55,584)	RV1 (N=6130)	RV5 (N=49,454)	P[a]
Series completed[b]; n (%)	**46,843 (84.3)**	**5577 (91.0)**	**41,266 (83.4)**	**<0.001**
Missing doses; n (%)	**8741 (15.7)**	**553 (9.0)**	**8188 (16.6)**	**<0.001**
Missing dose 2[c]		553 (9.0)	2321 (4.7)	
Missing dose 3[d]		NA	5867 (11.9)	

[a]Chi-square test; [b]Received correct number of valid doses for the series; [c]Infants who received only 1 dose; [d]Infants in the RV5 cohort who received dose 2, but not dose 3; NA, not applicable.

Compliance

- The proportion of infants with evidence of noncompliance due to either missed doses or incorrect dose timing was significantly greater in the RV5 cohort than in the RV1 cohort, regardless of which schedule was used in the analysis (Tables 4 and 5).
- Odds of compliance with the FDA-approved schedule for infants in the RV1 cohort were approximately double those in the RV5 cohort after adjustment (OR 2.0; 95%CI 1.9-2.2; *P*<0.001).
- A significantly greater proportion of infants in the RV1 cohort completed the full series according to the FDA-approved and harmonized dosing schedules (Tables 4 and 5).
- A total of 75.0% of infants in the RV1 cohort and 59.5% of infants in the RV5 cohort completed their series according to the appropriate FDA-approved schedule (*P*<0.001).

Table 4. Compliance with FDA-approved Schedules

	Total (N=55,584)	RV1 (N=6130)	RV5 (N=49,454)	P[a]
Fully-compliant series[b]; n (%[c])	**33,997 (61.2)**	**4598 (75.0)**	**29,399 (59.5)**	**<0.001**
Noncompliant; n (%[c])	**21,587 (38.8)**	**1532 (25.0)**	**20,055 (40.6)**	**<0.001**
All doses but incorrect dose timing	12,846 (23.1)	979 (16.0)	11,867 (24.0)	<0.001
Missing doses	8741 (15.7)	553 (9.0)	8188 (16.6)	<0.001

[a]Chi-square test.
[b]Received correct number of doses with all doses administered according to the brand-specific FDA-approved dosing schedule.
[c]Might not sum to 100% due to rounding.

Table 5. Compliance with the ACIP-recommended Harmonized Schedule

	Total (N=55,584)	RV1 (N=6130)	RV5 (N=49,454)	P[a]
Fully-compliant series[b]; n (%)	**42,909 (77.2)**	**5106 (83.3)**	**37,803 (76.4)**	**<0.001**
Noncompliant; n (%)	**12,675 (22.8)**	**1024 (16.7)**	**11,651 (23.6)**	**<0.001**
All doses but incorrect dose timing	3934 (7.1)	471 (7.7)	3463 (7.0)	0.050
Missing doses	8741 (15.7)	553 (9.0)	8188 (16.6)	<0.001

[a]Chi-square test.
[b]Received correct number of doses with all doses administered within windows defined by the ACIP-recommended harmonized dosing schedule.

DISCUSSION

- A large proportion of infants in the study sample completed their full series and most doses were administered within FDA-approved and ACIP-recommended windows.
  - Vaccine effectiveness was not assessed in this study. Previous studies have shown that infants who receive rotavirus vaccine benefit from protection against rotavirus gastroenteritis.[2-4]
- The cohort of infants that received the two-dose vaccine had a higher overall completion rate and completed the series faster than infants whose vaccination series required three doses. Infants whose series required fewer doses were more likely to adhere to the FDA-approved dosing schedule.
- No comparative head-to-head study of rotavirus vaccine efficacy has been conducted. Additional research is needed to compare effectiveness of the full two-dose RV1 series with effectiveness of a partial RV5 series and thus determine whether use of RV1 confers expected levels of protection sooner than use of RV5.
- The study cohorts were drawn from all eligible infants in the database who initiated a rotavirus vaccine series and thus reflect vaccine use in a real-life clinical setting. Although the cohort sizes are disproportionate, this does not affect the conclusions as the study is sufficiently powered to detect differences: given the fixed sample sizes in the two cohorts, α=0.05, and assuming a completion rate ranging from 75% to 90% in the RV5 cohort, we are able to detect a difference of +1.42% to +2.08% in the vaccination completion rate among infants in the RV1 cohort with 95% power (β=0.05).

Limitations

- Claims data are collected for payment, not research, and may not always accurately capture an individual's vaccine administration history.
- The study data are derived from a managed care population and therefore reflect health care utilization among infants with insurance coverage, but the findings might not be applicable to other populations.
- Infants were not randomly assigned to receive a specific vaccine brand. Because the cohorts were defined by the brand that was used in practice, selection bias (e.g., due to regional variation in brand availability) is possible.

CONCLUSIONS

Most infants who initiated a rotavirus vaccine series received the number of doses required for series completion and a high proportion received their doses according to the analyzed dosing schedules.

Among children vaccinated with the two-dose vaccine (RV1), the proportion that completed the series was greater (91.0% vs. 83.4%) and compliance with respective FDA-approved dosing schedules was higher (75.0% vs. 59.5%) than among those who received the three-dose vaccine (RV5).

Data from this study may indicate the potential for greater completion rates with a two-dose vaccine, but more study is needed.

REFERENCES

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