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Clinical and cost burden of rotavirus infection before and after introduction of rotavirus vaccines among commercially and Medicaid insured children in the United States

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Abbreviations: ACIP, Advisory Committee for Immunization Practices; CI, confidence interval; CPT, Current Procedural Terminology; ER, emergency room; HIPAA, Healthcare Insurance Portability and Accountability Act; ICD-9, International Classification of Disease Ninth Edition; PPPM, per-patient per-month; RV, rotavirus; SD, standard deviation; US, United States; WRE, winter residual excess method

This study aims to quantify clinical and economic burden of rotavirus (RV) infection pre- and post-vaccine introduction in commercially insured and Medicaid populations. Beneficiaries with continuous enrollment for ≥6 months while <5 years of age were identified separately in commercial (2000–2010) and Medicaid (2002–2009) claims databases. Commercial and Medicaid databases included 3 998 708 and 1 034 440 eligible children, respectively, observed from enrollment start date(s) to end of eligibility or 5-years-old. Rates of RV-coded and diarrhea-coded encounters and first RV episodes, and incremental cost of first RV episodes were calculated. In the post-vaccine period, rates per 10 000 person-years for RV-coded hospitalizations, outpatient visits and ER visits were 5.58 (95% CI, 5.37–5.80), 6.96 (95% CI, 6.75–7.20), and 4.85 (95% CI, 4.66–5.06), respectively (pre-vaccine, 16.67 [95% CI, 16.19–17.15], 13.20 [95% CI, 12.78–13.63], 11.26 [95% CI, 10.87–11.66], respectively), for commercially insured. In Medicaid the corresponding rates were 10.53 (95% CI, 9.60–11.56), 11.72 (95% CI, 10.73–12.80), and 9.11 (95% CI, 8.24–10.07) (pre-vaccine, 19.78 [95% CI, 19.14–20.45], 19.39 [95% CI, 18.75–20.05], 27.61 [95% CI, 26.84–28.40]). Incidence rate per 10 000 person-years for first RV episode pre- vs. post-vaccine were 27.03 (95% CI, 26.42–27.65) vs. 10.14 (95% CI, 9.86–10.44) in the commercially insured population and 37.71 (95% CI, 36.81–38.63) vs. 18.64 (95% CI, 17.37–19.99) in Medicaid. Incremental per-patient per-month cost of first RV episode was $3363 (95% CI, $3308-$3418) among commercially insured and $1831 (95% CI, $1768-$1887) in Medicaid. Since vaccine introduction clinical burden of RV disease decreased among children; costs associated with RV episodes remained significant across insured populations.

Introduction

Rotavirus (RV) is the most common cause of severe diarrhea among children less than 5 y of age worldwide, accounting for 453 000 deaths each year.[1] Although rarely fatal in the United States (US), RV has been a major cause of severe dehydration and hospitalization in children, thus incurring substantial healthcare resource utilization and costs. Before initiation of a routine infant RV vaccination program in 2006, nearly every child in the US was infected with RV by age 5 y (2.7 million episodes annually), resulting in approximately 55 000 to 70 000 hospitalizations, 410 000 outpatient visits, 205 000 to 272 000 emergency room (ER) visits annually, and total annual direct and indirect costs of approximately $1 billion.[2-6] Previous studies have shown that RV occurs primarily among children aged 4 to 23 mo, usually during winter (vs. summer) months.[6,7]

A pentavalent human-bovine reassortant RV vaccine (RotaTeq® [RV5]) was licensed for use in the US and recommended for routine vaccination of US children by the US Advisory Committee for Immunization Practices (ACIP) in February 2006.[8] By May 2007, vaccine coverage data reported that ~50% of infants aged 3 mo had received at least one dose of RV5.[9] A second RV vaccine (Rotarix® [RV1]) was licensed for use in the US in April 2008 and recommended by ACIP for routine use in June 2008. Both RV5 and RV1 are live, oral vaccines. RV5 contains 5 reassortment RVs which were developed from

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Table 1. Baseline characteristics of eligible children (less than 5-y-old)

Characteristic	Commercial N=3,999,708	Medicaid N=1,034,440
Eligible from birth, n (%)	1,191,474 (29.8)	504,098 (48.7)
Age at first continuous eligibility start, years	z	
Mean ± SD	1.52 ± 1.38	1.16 ± 1.38
Median (range)	1.51 (0.00-4.50)	0.51 (0.00-4.50)
Female, n (%)	1,950,781 (48.8)	502,858 (48.6)
Year of first insurance eligibility start date, n(%)		
2000	98,120 (2.5)	-
2001	69,475 (1.7)	-
2002	230,992 (5.8)	416,580 (40.3)
2003	246,298 (6.2)	133,389 (12.9)
2004	336,684 (8.4)	116,662 (11.3)
2005	334,449 (8.4)	109,663 (10.6)
2006	439,896 (11.0)	86,654 (8.4)
2007	461,242 (11.5)	50,262 (4.9)
2008	886,629 (22.2)	63,693 (6.2)
2009	596,122 (14.9)	57,537 (5.6)
2010	298,801 (7.5)	-
Type of health plan, n (%)		
Preferred provider organization	3,047,182 (76.2)	5,183 (0.5)
Non-capitated point-of-service	378,227 (9.5)	-
Consumer-driven health plan (CDHP)	193,566 (4.8)	-
Comprehensive	99,222 (2.5)	1,013,640 (98.0)
Exclusive provider organization	73,127 (1.8)	-
High deductible health plan (HDHP)	69,489 (1.7)	-
Unknown	137,895 (3.5)	15,617 (1.5)
Geographic region, n (%)		
South	1,659,879 (41.5)	-
North Central	1,089,872 (27.3)	-
West	681,923 (17.1)	-
Northeast	460,252 (11.5)	-
Unknown	106,782 (2.7)	-
Race, n (%)		
White	-	622,373 (60.2)
Black	-	241,251 (23.3)
Hispanic	-	113,292 (11.0)
Other	-	57,524 (5.6)
Duration of all continuous eligibility periods, years	1.8±1.1	1.8±1.1
Median (range)	1.49 (0.49-5.00)	1.34 (0.49-5.00

Notes: SD, standard deviation.

human and bovine strains; RV1 contains a human RV strain.[10] Both vaccines have demonstrated high efficacy (85–98%) against severe RV disease in clinical trials.[11,12]

Since the introduction of RV vaccines in 2006, the subsequent 3 RV seasons (i.e., 2007–2010) were consistently shorter and characterized by substantially fewer positive RV test results.[13,14] The burden of RV has declined accordingly, as characterized by sharp declines in diarrhea- and RV-related hospitalizations, outpatients visits, and ER visits among children less than 5 y of age including those age-ineligible to have received the vaccine, suggesting indirect benefits of vaccination.[15-23] However, few studies have quantified the economic burden of RV, particularly comparing costs before the introduction of RV vaccines with costs following its introduction.[20,24] In addition, few studies have assessed the burden of RV among children less than 5 y of age in the low-income Medicaid population, particularly during the post-vaccine era. This is particularly important in light of low vaccination rates and heavy disease burden in this population. Vaccination coverage statistics indicate that children living below the poverty level have lower coverage for RV vaccination.[25] One prior study of the Kids' Inpatient Database showed that while 40% of the children in the study were enrolled in Medicaid they accounted for nearly half of RV-associated hospitalizations.[26] Another study found that children who were enrolled in Medicaid or had no insurance were nearly 2 times more likely than other children to be hospitalized for RV.[27]

The present study used the Truven Commercial and Medicaid insurance claims databases to describe separately the clinical and economic burden of RV disease among children aged less than 5 y in each population, overall and also stratified by age and pre/post-RV vaccine availability.

Results

In the commercially insured population, a total of 3 998 708 eligible

Table 2. Utilization rates of RV-coded hospitalizations, outpatient visits, and ER visits in commercially insured and Medicaid populations, overall and stratified by age and pre/post-RV vaccine availability and calendar time

Incidence rate per 10 000 person-years (95% CI)						
	Commercial			Medicaid		
	Hospitalizations	Outpatient visits	ER visits	Hospitalizations	Outpatient visits	ER visits
Overall, <5 y	9.74 (9.51–9.96)	9.30 (9.08–9.52)	7.26 (7.06–7.45)	17.99 (17.43–18.56)	17.90 (17.35–18.47)	24.02 (23.38–24.68)
Pre[1]	16.67 (16.19–17.15)	13.20 (12.78–13.63)	11.26 (10.87–11.66)	19.78 (19.14–20.45)	19.39 (18.75–20.05)	27.61 (26.84–28.40)
Post[1]	5.58 (5.37–5.80)	6.96 (6.72–7.20)	4.85 (4.66–5.06)	10.53 (9.60–11.56)	11.72 (10.73–12.80)	9.11 (8.24–10.07)
Age						
<1 y						
Pre[1]	23.39 (21.93–24.94)	22.05 (20.64–23.56)	15.73 (14.54–17.01)	36.42 (34.45–38.50)	39.41 (37.36–41.58)	55.55 (53.11–58.11)
Post[1]	6.17 (5.61–6.78)	9.54 (8.84–10.30)	5.37 (4.85–5.94)	15.17 (13.07–17.62)	17.73 (15.44–20.36)	13.50 (11.52–15.81)
0 to <2 mo						
Pre[1]	9.36 (7.43–11.79)	6.89 (5.26–9.02)	5.33 (3.93–7.24)	20.72 (17.32–24.78)	16.40 (13.41–20.06)	22.10 (18.58–26.28)
Post[1]	4.58 (3.49–6.00)	5.98 (4.72–7.59)	4.05 (3.03–5.40)	11.60 (7.40–18.18)	15.26 (10.31–22.58)	9.76 (5.98–15.94)
2 to <4 mo						
Pre[1]	11.04 (8.88–13.73)	10.90 (8.76–13.58)	7.77 (5.99–10.07)	28.78 (24.74–33.48)	27.24 (23.32–31.82)	40.43 (35.59–45.93)
Post[1]	4.43 (3.38–5.82)	8.27 (6.78–10.09)	3.75 (2.79–5.04)	21.25 (15.52–29.08)	19.07 (13.69–26.56)	16.89 (11.88–24.01)
4 to <6 mo						
Pre[1]	21.10 (17.96–24.79)	17.97 (15.09–21.39)	12.69 (10.31–15.62)	32.78 (28.47–37.75)	40.42 (35.60–45.90)	49.93 (44.54–55.98)
Post[1]	3.36 (2.47–4.56)	8.93 (7.40–10.77)	3.69 (2.75–4.94)	11.87 (7.95–17.70)	12.85 (8.75–18.88)	8.90 (5.61–14.13)
6 to <12 mo						
Pre[1]	35.54 (32.87–38.44)	34.92 (32.27–37.79)	24.77 (22.56–27.21)	45.90 (42.75–49.28)	51.39 (48.05–54.96)	74.58 (70.54–78.86)
Post[1]	8.34 (7.42–9.38)	11.42 (10.33–12.63)	7.00 (6.16–7.95)	15.41 (12.54–18.95)	19.69 (16.40–23.64)	15.07 (12.23–18.57)
1 to <2 y						
Pre[1]	32.72 (31.27–34.25)	24.36 (23.11–25.68)	22.35 (21.15–23.61)	37.04 (35.08–39.10)	33.15 (31.30–35.10)	49.34 (47.07–51.71)
Post[1]	10.75 (10.11–11.44)	12.05 (11.37–12.78)	9.26 (8.66–9.90)	18.03 (15.40–21.10)	19.31 (16.58–22.48)	14.77 (12.41–17.58)
2 to <5 y						
Pre[1]	7.23 (6.83–7.64)	5.06 (4.73–5.41)	4.69 (4.38–5.03)	6.65 (6.17–7.17)	6.45 (5.98–6.97)	8.93 (8.37–9.53)
Post[1]	3.36 (3.16–3.58)	3.59 (3.38–3.82)	2.97 (2.78–3.18)	4.92 (4.07–5.95)	5.06 (4.20–6.10)	4.32 (3.53–5.29)

Notes: CI, confidence interval; RV, rotavirus; ER, emergency room;[1]Pre- and post-RV vaccine availability periods were defined as the time through January 1, 2007 and the time after that date, respectively.

Table 2. Utilization rates of RV-coded hospitalizations, outpatient visits, and ER visits in commercially insured and Medicaid populations, overall and stratified by age and pre/post-RV vaccine availability and calendar time (continued)

Calendar time						
7/2000–6/2001	19.13 (16.63–21.99)	9.42 (7.72–11.49)	5.73 (4.44–7.39)	-	-	-
7/2001–6/2002	18.83 (16.97–20.89)	11.95 (10.49–13.62)	10.58 (9.21–12.15)	-	-	-
7/2002–6/2003	16.28 (14.96–17.72)	12.45 (11.30–13.71)	9.07 (8.10–10.16)	17.30 (16.03–18.68)	19.04 (17.70–20.48)	22.76 (21.29–24.33)
7/2003–6/2004	20.26 (19.00–21.61)	14.47 (13.41–15.61)	13.11 (12.10–14.21)	19.42 (18.07–20.89)	22.40 (20.94–23.97)	26.81 (25.21–28.52)
7/2004–6/2005	20.14 (19.03–21.32)	15.90 (14.92–16.96)	15.09 (14.12–16.11)	19.21 (17.84–20.70)	17.72 (16.39–19.14)	29.42 (27.70–31.24)
7/2005–6/2006	18.55 (17.56–19.60)	16.63 (15.69–17.62)	14.76 (13.88–15.70)	29.17 (27.44–31.01)	23.82 (22.26–25.49)	43.29 (41.17–45.52)
7/2006–6/2007	13.29 (12.52–14.11)	14.12 (13.33- 14.96)	10.75 (10.06–11.49)	9.85 (8.62–11.25)	12.04 (10.67–13.58)	8.94 (7.77–10.28)
7/2007–6/2008	4.78 (4.39–5.21)	6.81 (6.33 – 7.32)	4.27 (3.90–4.68)	7.69 (6.33–9.34)	8.37 (6.95–10.09)	6.17 (4.96–7.67)
7/2008–6/2009	6.37 (5.96–6.80)	8.39 (7.93 – 8.89)	5.85 (5.46–6.26)	9.98 (8.48–11.74)	10.46 (8.92 – 12.26)	8.33 (6.97–9.95)
7/2009–6/2010	0.94 (0.78–1.13)	1.73 (1.51–1.98)	0.89 (0.74–1.07)	-	-	-

Notes: CI, confidence interval; RV, rotavirus; ER, emergency room;[1]Pre- and post-RV vaccine availability periods were defined as the time through January 1, 2007 and the time after that date, respectively.

children were identified, 30% of whom were considered eligible from birth (**Table 1**). At their first continuous eligibility start, these children were on average 1.52 (standard deviation [SD]: 1.38, median 1.51) years old; 67% were eligible on or after 2006. Children were on average observed for 1.8 (SD: 1.1) years.

In the Medicaid population, a total of 1 034 440 eligible children were identified, 49% of whom were considered eligible from birth (**Table 1**). At their first continuous eligibility start, these children were on average 1.16 (SD: 1.38, median 0.51) years old; 25% were eligible on or after 2006. Children were on average observed for 1.8 (SD: 1.1) y.

Clinical burden

Eligible children less than 5 y of age in the commercially insured population were observed for a total of 7 405 228 person-years over the years 2000–2010. In the Medicaid population, eligible children less than 5 y of age were observed for a total of 2 172 990 person-years over 2002–2009. **Table 2** summarizes the RV-related healthcare resource utilization. Overall, RV-coded utilization rates per 10 000 person-years were 9.74 (95% CI, 9.51–9.96) for hospitalizations, 9.30 (95% CI, 9.08–9.52) for outpatient visits, and 7.26 (95% CI, 7.06–7.45) for ER visits in the commercially insured population. In the Medicaid population, the RV-related utilization rates per 10,000 person-years were 17.99 (95% CI, 17.43–18.56) for hospitalizations, 17.90 (95% CI, 17.35–18.47) for outpatient visits, and 24.02 (95% CI, 23.38–24.68) for ER visits. As shown in **Table 2**, utilization rates for children less than 5-y-old in the commercially insured population declined significantly by 67% from 16.67 (95% CI, 16.19–17.15) to 5.58 (95% CI, 5.37–5.80) per 10 000 person-years) for hospitalizations, 47% from 13.20 (95% CI, 12.78–13.63) to 6.96 (95% CI, 6.75–7.20) per 10,000 person-years for outpatient visits, and 57% from 11.26 (95% CI, 10.87–11.66) to 4.85 (95% CI, 4.66–5.06) per 10 000 person-years for ER visits from the pre- to post-vaccine period. The corresponding percentage declines in the Medicaid population were 47% from 19.78 (95% CI, 19.14–10.53) to 20.45 (95% CI, 9.60–11.56) per 10 000 person-years for hospitalizations, 40% from 19.39 (95% CI, 18.75–20.05) to 11.72 (95% CI, 10.73–12.80) per 10 000 person-years for outpatient visits, and 67% from 27.61 (95% CI, 26.84–28.40) to 9.11 (95% CI, 8.24–10.07) per 10 000 person-years for ER visits. In both populations, the rate of hospitalization, outpatient visits and ER visits decreased among all age subgroups between the pre- and the post-vaccination periods.

The lower panel of **Table 2** shows the rates of RV-related resource utilization across the calendar years 2000–2010. Since the introduction of the vaccine in 2006–2007, the resource utilization has decreased at all points of care among both populations. Among the commercially insured population, the decline began in the 2006–2007 season, and the steepest decline for hospitalization, ER, and outpatient visits was in the 2009–2010 season. The 2008–2009 season did experience an increase in resource utilization for all points of care relative to the prior season. Correspondingly, for Medicaid patients the decline in RV-related resource utilization began in 2006–2007, and this season had the steepest decline for ER, hospitalization and outpatient visits. In this population, the 2008–2009 season also had an increase in resource utilization for all points of care relative to the prior season.

As shown in **Table 3**, among those less than 5 y of age in the commercially insured population, between 2000–2010 the rate of diarrhea-coded hospitalization, outpatient visits and ER visits had slight yet statistically significant reductions between the pre- and post-vaccine introduction periods. Correspondingly, among those in the Medicaid population between 2002–2009 the rate of hospitalization and ER visits had a slight yet statistically significant overall reduction between the pre- and post-vaccine introduction period. The rate of outpatient visits that were diarrhea-related increased between the pre- and post-vaccination periods in the Medicaid population. The lower panel of **Table 3** shows the rates of diarrhea-related resource utilization across the calendar years 2000–2010. Since the introduction of the vaccine in 2006–2007, the resource utilization has decreased at all points of care among both populations. Among the commercially insured population, the decline began in the 2006–2007 season; the 2008–2009 season did experience an increase in resource utilization for all points of care relative to the prior season. Correspondingly, for Medicaid patients the decline in diarrhea-related resource utilization began in 2006–2007, and the 2008–2009 season in this population also had an increase in resource utilization for all points of care relative to the prior season.

Results from the winter residual excess (WRE) method showed that for the overall time period 39.0%, 15.7%, and 30.4% of diarrhea-coded hospitalizations, outpatient visits, and ER visits, respectively, were attributable to RV among the commercially insured. The proportion of diarrhea-coded events attributable to RV decreased from the pre-vaccine period to the post-vaccine period from 48.9% to 29.6%, from 21.2% to 12.3%, and from 38.6% to 25.2%, for hospitalizations, outpatient visits, and ER visits, respectively, in this population. Similar results were found in Medicaid.

Overall incidence rates of first RV episodes were 16.47 (95% CI, 16.18–16.77) per 10000 person-years in the commercially insured population and 34.02 (95% CI, 33.25–34.80) per 10000 person-years in the Medicaid population (**Table 4**). In both populations, overall incidence rate decreased significantly after the introduction of RV vaccines. The incidence rate also decreased for each age-specific category.

Economic burden

Table 5 describes the per-patient per-month (PPPM) cost differences between first RV episodes and their matched control. Overall, first RV episodes in the commercially insured population were significantly more expensive than similar controls without RV by $3363 (95% CI, $3308-$3418) PPPM. The corresponding PPPM cost difference in the Medicaid population, also significant, was $1831 (95% CI, $1768-$1887). Most of the PPPM cost differences were due to differences in hospitalization costs. There were no significant differences in the cost of RV episodes between the pre- and post- periods.

Discussion

Findings from the present analysis of RV burden among 2 differently insured populations, one by commercial private insurance and one by government Medicaid, suggest that the clinical burden of RV disease among children less than 5 y of age has reduced since the 2005–2006 season. This trend was observed in all 4 outcomes of RV burden, namely incidence rates of RV-coded encounters, diarrhea-coded encounters, episodes of first RV infection and diarrhea-coded encounters attributable to RV. In both populations, the clinical burden of RV appeared to be highest among children less than 2 y of age. Noteworthy, this is the first study that examined these effects in a low socio-economic segment of the US population.

The present study findings confirmed other reports of a decline in RV activity in the US after the introduction of RV vaccine.[15-23] In the current study, in both populations, the incidence of RV-coded encounters among children less than 5 y of age declined after the introduction of RV vaccines. In the commercially insured population, rates of RV-coded hospitalizations, outpatient visits, and ER visits declined by 67%, 47%, and 57%, respectively. Similar results were reported by Cortes et al.[20] in an analysis of the commercially insured population. In that study, the percent reduction in hospitalizations for RV-coded diarrhea for 2007–2008 vs. 2001–2006 and for 2008–2009 vs. 2001–2006 were 75% and 60%, respectively, in the commercially insured population. In the current study, in the Medicaid population, rates of RV-coded hospitalizations, outpatient visits, and ER visits declined by 47%, 40%, and 67%, respectively. Cortes et al.[20] reported declines in diarrhea-associated hospitalization rates in the commercially insured population of 33% and 25% for 2007–2008 and 2008–2009, respectively, compared with the pre-vaccination period. In the current study, diarrhea-associated hospitalization rates declined in the commercially insured and Medicaid populations by 38% and 7%, respectively, in the pre- vs. post-vaccination periods. Our study found modest reductions in the diarrhea-associated ER visit rates in the pre- vs. post-vaccination periods and slightly more outpatient visits in the Medicaid population. Cortes et al.[20] reported similar modest reduction in the ER visit rate and higher outpatient visit rates for some age groups in the pre- vs. post-vaccination periods. Noteworthy, in the current study descriptive results are reported for the commercially and Medicaid insured populations which may be economically separated populations but not geographically separated populations. The experience of RV infection and vaccination in one population may affect RV disease in the other through RV transmission or influence on herd immunity (i.e., when unvaccinated persons have less likelihood of infection because vaccinated persons do not contract and transmit disease).

The WRE analysis showed that the estimated proportion of diarrheal disease attributable to RV declined from the pre-vaccine to post-vaccine period for both populations. This method assumes that the excess of diarrheal cases in the winter months is due to RV. Norovirus activity also has a characteristic wintertime seasonality,[28] so some of the excess diarrheal cases counted as RV in this analysis may have actually been due to other pathogens such as norovirus. However, if norovirus and other non-RV diarrheal pathogens with wintertime seasonality remained relatively constant over the years then the difference in WRE cases

Table 3. Utilization rates of diarrhea-coded hospitalizations, outpatient visits, and ER visits in commercially insured and Medicaid populations, overall and stratified by age and pre/post-RV vaccine availability

	Incidence rate per 10 000 person-years (95% CI)					
	Commercial			Medicaid		
	Hospitalizations	Outpatient Visits	ER Visits	Hospitalizations	Outpatient Visits	ER Visits
Overall <5 y	44.19 (43.71–44.67)	1458.87 (1456.12–1461.62)	198.18 (197.17–199.20)	83.68 (82.47–84.91)	1816.78 (1811.12–1822.45)	621.4 (618.19–624.82)
Pre[1]	57.55 (56.67–58.45)	1496.03 (1491.48–1500.58)	203.88 (202.20–205.56)	84.8 (83.54–86.27)	1788.37 (1782.12–1794.65)	637.42 (633.69–641.17)
Post[1]	36.17 (35.63–36.73)	1436.58 (1433.13–1440.04)	194.76 (193.49–196.04)	78.66 (76.03–81.39)	1934.79 (1921.56–1948.11)	555.34 (548.27–562.50)
Age						
<1 y						
Pre[1]	89.92 (87.01–92.92)	2407.37 (2392.15–2422.68)	294.04 (288.76–299.43)	160.44 (156.24 164.75)	2870.74 (2852.81–2888.79)	1041.5 (1030.72–1052.39)
Post[1]	59.75 (57.95–61.60)	2176.44 (2165.44–2187.49)	274.45 (270.56–278.39	138.14 (131.4 -145.16)	2666.83 (2636.94–2697.06)	812.99 (796.56–829.76)
0 to <2 mo						
Pre[1]	84.65 (78.39–91.41)	1540.03 (1512.55–1568.02)	184.12 (174.77–193.96)	171.79 (161.44–182.81)	1766.97 (1733.07–1801.54)	635.72 (615.52–656.59)
Post[1]	76.64 (71.72–81.91)	1281.11 (1260.47–1302.09)	175.46 (167.93–183.33)	194.07 (173.87–216.62)	1706.36 (1644.27–1770.79)	563.90 (528.69–601.46)
2 to <4 mo						
Pre[1]	65.29 (59.70–71.41)	2058.03 (2025.46–2091.12)	211.42 (201.15–222.21)	166.69 (156.54–177.50)	2628.99 (2587.73–2670.92)	899.06 (875.06–923.72)
Post[1]	57.29 (53.11–61.78)	1880.28 (1855.63–1905.26)	218.83 (210.52–227.46)	156.90 (139.79–176.11)	2369.32 (2299.94–2440.79)	679.90 (643.21–718.69)
4 to <6 mo						
Pre[1]	73.72 (67.63–80.35)	2261.27 (2226.35–2296.74)	261.50 (249.80–273.75)	148.10 (138.59–158.27)	2834.50 (2791.82–2877.83)	1021.60 (996.11–1047.75)
Post[1]	47.75 (44.03–51.79)	2072.01 (2046.63–2097.70)	251.13 (242.39–260.18)	114.21 (100.39–129.93)	255.24 (2387.90–2524.49)	783.15 (745.51–822.68)
6 to <12 mo						
Pre[1]	108.89 (104.13–113.88)	2988.86 (2963.46–3014.48)	389.27 (380.17–398.58)	158.64 (152.69–164.83)	3354.91 (3327.13–3382.93)	1240.72 (1223.87 -1257.80)
Post[1]	59.24 (56.69–61.91)	2622.77 (2605.46–2640.18)	336.12 (329.96–342.39)	124.85 (116.10 -134.25)	3103.17 (3058.32–3148.68)	935.06 (910.59–960.20)

Notes: CI, confidence interval; RV, rotavirus; ER, emergency room. [1]Pre- and post-RV vaccines were defined as before and on/after 01/01/2007, respectively.

Table 3. Utilization rates of diarrhea-coded hospitalizations, outpatient visits, and ER visits in commercially insured and Medicaid populations, overall and stratified by age and pre/post-RV vaccine availability (continued)

1 to <2 y						
Pre[1]	94.09 (91.60–96.64)	2351.68 (2339.10–2364.33)	320.10 (315.48–324.78)	122.53 (118.93–126.24)	2555.51 (2538.87–2572.26)	909.70 (899.79–919.72)
Post[1]	55.25 (53.76–56.77)	2284.05 (2274.39–2293.74)	297.56 (294.09–301.07)	96.53 (90.19–103.33)	2772.88 (2737.90–2808.30)	753.44 (735.31–772.01)
2 to <5 y						
Pre[1]	32.28 (31.43–33.14)	889.80 (885.32–894.30)	128.14 (126.45–129.86)	42.15 (40.91–43.43)	1105.81 (1099.37–1112.29)	387.56 (383.76–391.41)
Post[1]	22.62 (22.07–23.17)	928.93 (925.41–932.47)	134.43 (133.09–135.78)	40.01 (37.44–42.76)	1225.03 (1210.40–1239.83)	337.81 (330.18–345.63) *
Calendar time						
7/2000–6/2001	75.43 (70.31–80.93)	1645.46 (1620.87 1670.42)	198.05 (189.64–206.83)	-	-	-
7/2001–6/2002	69.07 (65.43–72.92)	1524.37 (1506.87–1542.07)	198.28 (192.03–204.73)	-	-	-
7/2002–6/2003	60.53 (57.93–63.25)	1488.77 (1475.64–1502.02)	202.80 (197.98–207.72)	88.84 (85.89–91.89)	1854.34 (1840.69–1868.10)	648.02 (639.96–656.17)
7/2003–6/2004	63.18 (60.92–65.53)	1515.86 (1504.62–1527.18)	216.85 (212.62–221.16)	87.00 (84.07–90.03)	1908.51 (1894.61–1922.52)	642.19 (634.14–650.33)
7/2004–6/2005	62.20 (60.22–64.25)	1496.00 (1486.14–1505.92)	217.47 (213.73–221.27)	77.99 (75.16–80.93)	1662.88 (1649.62–1676.24)	612.98 (604.95–621.11)
7/2005–6/2006	56.46 (54.72–58.26)	1558.35 (1549.08–1567.68)	217.63 (214.18–221.14)	89.85 (86.77–93.04)	1733.93 (1720.21–1747.75)	678.99 (670.43–687.66)
7/2006–6/2007	51.15 (49.62–52.72)	1546.40 (1537.89–1554.95)	218.65 (215.46–221.88)	70.94 (67.50–74.55)	1755.08 (1737.64–1772.70)	559.22 (549.41–569.21)
7/2007–6/2008	35.51 (34.40–36.65)	1469.15 (1461.95–1476.37)	186.29 (183.74–188.88)	70.33 (65.94–75.02)	1872.94 (1849.68–1896.49)	487.23 (475.43–499.31)
7/2008–6/2009	41.48 (40.43–42.57)	1553.80 (1547.26–1560.37)	220.49 (218.03–222.97)	84.08 (79.50–88.93)	1992.03 (1969.22–2015.11)	594.97 (582.57–607.65)
7/2009–6/2010	24.73 (23.86–25.62)	1239.38 (1233.17–1245.63)	161.77 (159.53–164.04)	-	-	-

Notes: CI, confidence interval; RV, rotavirus; ER, emergency room. [1]Pre- and post-RV vaccines were defined as before and on/after 01/01/2007, respectively.

pre-vaccine and post-vaccine could be attributable to RV and the availability of the vaccine during the later time.

In addition as reported in previous studies, this study also noted that the disease burden did increase in the 2008–2009 season relative to the prior season. Payne et al.[18] speculated this may have occurred because some unvaccinated children were unexposed to RV in 2008 due to vaccination of other children. These unvaccinated children then gained a single-year deferral of RV infection. With vaccination and a lower number of susceptible individuals in the population, it can take time for a sufficient number of susceptible individuals in the population to accumulate and have the ability to acquire and transmit infection to others. Changes in billing coding practices over the years could also affect the measurement of disease burden in a study conducted

Table 4. Incidence rates of first RV episodes in commercially insured and Medicaid populations, overall and stratified by age and pre/post-RV vaccine availability

Incidence rate per 10 000 person-years (95% CI)		
	Commercial	**Medicaid**
Overall	16.47 (16.18–16.77)	34.02 (33.25–34.80)
Pre[1]	27.03 (26.42–27.65)	37.71 (36.81–38.63)
Post[1]	10.14 (9.86–10.44)	18.64 (17.37–19.99)
Age		
<1 y		
Pre[1]	43.32 (41.32–45.42)	78.46 (75.54–81.49)
Post[1]	13.65 (12.81–14.55)	29.29 (26.31–32.62)
0 to <2 mo		
Pre[1]	19.09 (16.25–22.43)	41.62 (36.71–47.20)
Post[1]	12.74 (10.83–14.99)	37.52 (29.26–48.13)
2 to <4 mo		
Pre[1]	23.74 (20.46–27.54)	59.85 (53.89–66.47)
Post[1]	9.89 (8.24–11.86)	23.96 (17.83–32.20)
4 to <6 mo		
Pre[1]	35.41 (31.27–40.10)	74.90 (68.22–82.24)
Post[1]	10.90 (9.19–12.91)	24.24 (18.32–32.07)
6 to <12 mo		
Pre[1]	65.33 (61.61–69.22)	99.39 (94.68–104.32)
Post[1]	16.30 (15.0–17.73)	30.39 (26.23–35.22)
1 to <2 y		
Pre[1]	50.53 (48.71–52.42)	64.76 (62.14–67.48)
Post[1]	18.33 (17.49–19.22)	29.86 (26.41–33.75)
2 to <5 y		
Pre[1]	10.91 (10.42–11.42)	11.92 (11.26–12.61)
Post[1]	5.53 (5.26–5.81)	7.97 (6.86–9.26)

Notes:CI, confidence interval; RV, rotavirus. [1]Pre- and post-RV vaccine availability periods were defined as the time through January 1, 2007 and the time after that date, respectively.

with insurance claims data. In addition, a change in the catchment population over the years could introduce variation in the disease burden.

In both the commercially insured and Medicaid populations, PPPM costs associated with RV episodes were consistently higher relative to their matched control episodes for hospitalizations, outpatient visits, ER visits, and pharmacy claims. Compared with the pre-vaccination period, the incremental costs associated with RV episodes during the post-vaccination period was not significantly different in the commercially insured population. This finding, coupled with the significantly lower RV episode incidence rate over time, suggests important savings in overall RV treatment costs in the post-vaccine period. For example, in a population of 10 000 commercially insured individuals, the excess annual cost associated with RV was estimated at $91 037 in the pre-vaccine period and $34 010 in the post-vaccine period. Notably, however, the cost of vaccination nor cost of long-term adverse events were included in these calculations, so this does not constitute a cost-benefit analysis.

In the Medicaid population, the difference in total cost between an RV and control episode during the post-vaccination period was slightly higher than in the pre-vaccination period for the overall population ($2219 (95% CI, $2008-$2,443) PPPM vs. $1785 (95% CI, $1728-$1849) PPPM). The difference in PPPM costs between RV episode and control episode was higher for the post- vs. pre-vaccine period in Medicaid for those <1 y old but not for those 1- < 2-y-old or 2- < 5-y-old. Of the 3 age strata (<1-y-old, 1- < 2-y-old, 2- < 5-y-old), in the Medicaid population more RV cases occurred among those < 1-y-old (44% in both pre- and post-vaccine periods). Thus, the difference in PPPM costs between an RV episode and control episode for the overall population was influenced more by the costs among RV cases < 1-y-old, and this could be driving the higher post- vs. pre-vaccine period difference in cost between an RV and control episode that is observed. In contrast, in the commercially insured population, there were more RV cases among those 1- to 2-y-old (44% pre-vaccine and 41% post-vaccine) compared with other age strata, and the PPPM costs between an RV episode and control episode was higher pre- vs. post-vaccine for this age stratum in this population. Of note, only 2 y of post-vaccine data were available in the Medicaid analysis, resulting in smaller numbers of RV events and less precision to estimate the incremental cost associated with RV during that period. Nevertheless, given the sharp decline observed in RV episode rate over time, the excess annual cost associated with RV in a population of 10 000 Medicaid individuals was estimated at $67 312 in the pre-vaccine period and $41 362 in the post-vaccine period. This finding also suggests important savings in overall RV treatment costs during the post-vaccine period for the Medicaid population.

Some limitations of the present study should be considered. First, since population RV vaccine coverage was not assessed, we could only examine overall vaccine benefits, including direct (i.e., direct protection of vaccinated persons that did not contract disease) and indirect (i.e., indirect protection of unvaccinated persons because vaccinated persons did not contract and transmit disease) benefits. In this study, the correlation between vaccine coverage, or lack thereof, and RV disease was not assessed. Second, we conducted stratified analysis by age and pre/post-RV vaccine availability. There could be other strata of interest where effect modifications by RV vaccination could differ. Third, we examined data from only 2 and 3 post-vaccine RV seasons in the commercially insured (2007–2010) and Medicaid (2007–2009) populations, respectively, and cannot be certain that observed changes were due solely to vaccine use. Secular trends in the incidence of RV and other diarrheal pathogens could affect our findings. Fourth, as with all claims database analyses, ICD-9 codes were used to identify diagnoses; these codes may not reflect confirmed clinical diagnoses and lack information to assess severity of illness. RV infections may have been coded under more general diagnosis codes without linkage to RV. Although the Truven

claims databases offer the largest convenience sample available in proprietary databases, with more than 180 million unique patients from over 300 contributing employers since 1995, the findings in the current study were based on the population of individuals seeking healthcare and thus may not reflect the true burden of disease in the entire population. Moreover, medical services obtained outside of a patient's plan are not captured in a claims database, therefore, resource utilization and costs in this study may be underestimated. Furthermore, for children who enrolled after birth, the first RV episode captured in the claims data may not actually be the first RV episode experienced. Finally, since data from separate continuously eligible periods from the same child may have been included it is possible that a child's subsequent RV episode was counted toward the calculation of first RV episode incidence if the child had a subsequent RV episode in the second or later continuously eligible period.

Findings from the present claims database analysis suggest that the clinical burden of RV disease has decreased in both the commercially insured and Medicaid populations since the introduction of the vaccine in 2006. Most notably, reductions in RV disease burden since vaccine introduction were observed in the Medicaid population where the vaccine coverage is lower and disease burden higher than other segments of the US population.

Methods

Data source

Data from the 2000–2010 Truven Commercial Claims and Encounters and the 2002–2009 Truven Medicaid databases were analyzed separately. The years 2010 and 2009 were the most recent years of data available for the study with Commercial and Medicaid data, respectively. Truven data were derived from insurance claims and contained de-identified information from various public and private health plans, including comprehensive, exclusion provider organizations, health maintenance organizations, non-capitated point-of-service, preferred provider organizations, consumer-driven health plans, and high deductible health plans.

The Truven Commercial database contained claims from approximately 100 employers and a number of health plans. Between 2000 and 2010, data from approximately 8 million children under 5 y of age were captured. The Truven Medicaid database contained the pooled healthcare experience of approximately 28 million Medicaid enrollees from 11 states. Between 2002 and 2009, data from approximately 4.5 million children under 5 y of age were captured. In both databases, variables included patient demographics, date of service, place of service, International Classification of Disease Ninth Edition (ICD-9) codes, Current Procedural Terminology (CPT) codes, length of hospital stay, and cost data in the form of payments made by insurers and patients to providers (physicians and hospitals).

Approval for this study was obtained from the Institutional Review Board of Rutgers University.

Table 5. PPPM cost differences of first RV episodes relative to their matched control episodes in commercially insured and Medicaid populations, overall and stratified by age and pre/post-RV vaccine availability

PPPM cost differences (incremental cost of RV episodes)[1,2]				
	Commercial		Medicaid	
	Mean	(95% CI)	Mean	(95% CI)
Overall	$3363	($3308–$3418)	$1831	($1768–$1887)
Hospitalizations	$2484	($2429–$2541)	$1374	($1318–$1426)
Outpatient visits	$416	($397–$434)	$166	($158–$174)
ER visits	$430	($414–$445)	$214	($205–$224)
Pharmacy	$34	($30–$37)	$76	($67–$85)
Age				
<1 y				
Pre[1]	$3368	($3191–$3523)	$1712	($1629–$1806)
Post[1]	$2992	($2782–$3216)	$2266	($1884–$2629)
0 to <2 mo				
Pre[1]	$3839	($3080–$4607)	$2448	($1986–$2938)
Post[1]	$3355	($2735–$4008)	$2769	($1348–$3882)
2 to <4 mo				
Pre[1]	$3153	($2550–$3697)	$1818	($1539–$2099)
Post[1]	$2703	($2051–$3407)	$2083	($1339–$2738)
4 to <6 mo				
Pre[1]	$3717	($3235–$4201)	$1819	($1587–$2100)
Post[1]	$2623	($2074–$3216)	$3112	($1973–$4494)
6 to <12 mo				
Pre[1]	$3266	($3072–$3449)	$1556	($1463–$1666)
Post[1]	$3045	($2791–$3324)	$1911	($1544–$2301)
1 to <2 y				
Pre[1]	$3416	($3299–$3517)	$1774	($1700–$1861)
Post[1]	$3427	($3295–$3581)	$2146	($1813–$2532)
2 to <5 y				
Pre[1]	$3401	($3267–$3525)	$1838	($1713–$1970)
Post[1]	$3768	($3617–$3919)	$2298	($1921–$2727)

Notes: CI, confidence interval; PPPM, per-patient per-month; RV, rotavirus; SD, standard deviation. Costs are in 2010 USD.[1]Pre- and post-RV vaccine availability periods were defined the time through January 1, 2007 and the time after that date, respectively; [2]The incremental cost analysis tests the null hypothesis of cost difference equal to $0 between RV and control episodes.

Study population

To be included in the study population, beneficiaries must have continuously received both medical and pharmacy benefits (to ensure complete claims data) for at least 6 mo while aged less than 5 y. These children formed the eligible population for this study. To be compliant with the Health Insurance Portability and Accountability Act (HIPAA) only birth year was available in the data. Due to the absence of exact birth dates in Truven

insurance claims data the enrolment date was used as a proxy for birth date when year of first enrolment and birth year were equivalent. Otherwise, the birth date was assumed to be June 30th of the birth year. Beneficiaries who enrolled in capitation-based health plans and therefore may have incomplete claims were excluded.

Since breaks in eligibility were possible, all periods of continuous eligibility lasting at least 6 mo in duration were included in the analysis. Thus, an individual may have contributed more than one continuous period to the study. All eligible beneficiaries in each population were analyzed as one study cohort, among which the burden of RV was described. However, the burden of RV among children aged less than 1 y were calculated only among children who were continuously eligible from birth as their birth dates were more accurately estimated from their eligibility start date.

Study design

To evaluate the clinical burden of RV, a retrospective, longitudinal, open-cohort study design was used. Each eligible child was observed from his/her enrolment date(s) to end of continuous eligibility (due to disenrollment, data cut-off, or death) or 5 y of age (imputed age based on year of birth), whichever occurred first.

To evaluate economic burden of the first RV episode a matched-cohort design was used. Children with RV were matched to 3 controls without RV to quantify the incremental costs attributable to first RV episodes. Control patients were randomly selected from all eligible children with same year of birth, gender, state of residence, and calendar year at eligibility start as the child with the RV episode. The only clinical condition for selecting a control period was that no RV claim occurred during that time. Potential controls had continuous eligibility at least as long as the lag time between the eligibility start and index date of the matched RV episode. The index date (start date for the observation) of the matched control was imputed so that the duration from the eligibility start date to the imputed index date was equal in duration from the eligibility start date to the index date of the matched RV episode. Controls had no RV claims from the imputed index date to 2 mo following the imputed index date. Each matched control was followed from the imputed index date to the earliest occurrence of 2 mo after the imputed index date, end of continuous eligibility (i.e., due to disenrollment, data cut-off, or death), or 5 y of age. This period was used to calculate costs during a non-RV control period.

Study outcomes

We described the clinical burden of RV by calculating the rates of 3 events: RV-coded encounters (i.e., hospitalizations, outpatient visits, and ER visits), diarrhea-coded encounters, and first episodes of RV infection. We also estimated the proportion of diarrhea-coded events attributable to RV. RV-coded encounters were identified by claims with the specific ICD-9 code for RV (008.61 — Enteritis due to rotavirus) as done in prior studies.[20] An encounter identified with a RV diagnosis as the primary discharge diagnosis or one of 15 non-primary discharge diagnoses in the inpatient admission table was classified as a RV-related hospitalization. An encounter identified with a RV diagnosis in one of the 2 diagnosis fields in the outpatient-services table was classified as a RV-related outpatient visit. If a patient had an ICD-9 code for RV disease on the same day as a CPT code for RV vaccine in an outpatient setting, the ICD-9 code was not counted as a case of RV disease. In this event it was assumed that the claim with the ICD-9 code for RV disease appeared due to the event of the vaccination for RV and not RV disease itself. An encounter was classified as an RV-related ER visit (i.e., neither hospitalization nor outpatient visit) if 'urgent care facility' or 'emergency room' was specified in either the inpatient or outpatient services table. Patients evaluated in more than one setting for the same RV episode may have had multiple encounters recorded in the database for the one RV episode.

Diarrhea-coded encounters were identified by claims with the non-specific ICD-9 codes for diarrhea: 009.0–009.3 (Presumed infectious gastroenteritis), 558.9 (Presumed noninfectious gastroenteritis), 787.91 (Diarrhea), 008.6–008.8 (Viral gastroenteritis), 001.0–005.9 (excluding 003.2) and 008.0–008.5 (Bacterial gastroenteritis), and 006.0–007.9 (excluding 006.3–006.6) (Parasitic gastroenteritis).

Diarrhea-coded encounters attributable to RV were determined by using the WRE method. This method is used to estimate the proportion of diarrhea cases attributable to RV. In this method, the winter excess of diarrhea-coded encounters attributable to RV was calculated as the difference in diarrhea-coded encounters between the winter-spring peak of RV, occurring in the 6 mo between November and April, and the summer-fall baseline between May and October.[18,22,23]

RV-coded claims dated within 14 d of each other were further used to identify an episode of RV infection. Each RV episode was assumed to last from 14 d before the first RV-coded claim of the episode to 14 d after the last RV-coded claim of the episode, unless truncated by start or end of continuous eligibility.

We assessed the incremental cost of RV episodes by calculating the total PPPM cost of first RV episodes and comparing them to the total PPPM cost of matched non-RV control periods. The total PPPM cost of first RV episode was calculated by summing all costs occurring during the duration of the first RV episode and dividing this by the duration of the first RV episode.

Statistical analysis

For all eligible children, characteristics at first continuous eligibility start, including age, gender, calendar year, health plan type, and state of residence (for the commercially insured population) or race (for Medicaid population) and duration of all continuous eligibilities were described. Frequencies and proportions were reported for categorical variables while means, medians, and ranges were reported for continuous variables.

Rates of RV-coded encounters, diarrhea-coded encounters and first RV episodes were calculated by dividing the total number of each event by the total person-years of observation. This person-time approach was used to account for different lengths of observation among study subjects in a non-experimental setting. Poisson probability density function was used to generate the 95% confidence intervals (CIs) for the incidence rates.

The proportion of diarrhea-coded events attributable to RV was determined by dividing the number of diarrhea-coded events attributable to RV by the number of diarrhea-coded events.

All claims dated between the start and end of each episode were included in the calculation of the PPPM cost of first RV episodes and their matched controls. Since cost data are often not normally distributed, the bootstrapping method was used to estimate the 95% CI of the difference in PPPM costs between RV episodes and their matched control episodes. With the bootstrapping method, the RV episodes and their matched control episodes were sampled with replacement 500 times. Within each of the 500 resamples a linear model was used to calculate the difference in PPPM cost for an RV episode relative to matched control episodes. The PPPM cost differences from the 500 resamples were then used to determine the 95% CI using the percentile bootstrap method. A 95% CI that excluded zero indicated a significant difference in PPPM costs between RV episodes and their matched control episodes.

All analyses were stratified by age and time before/after January 1, 2007, which marked the first full year when RV vaccination was available. Costs were inflation-adjusted to 2010 US dollars based on the medical care component of the Consumer Price Index. All analyses were performed using SAS software version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Disclosure of Potential Conflicts of Interest

P.L. and M.D. are employees of Analysis Group, Inc., which has received research grants from GSK for this study as well as other studies. G.K. is employed by and holds restricted shares in the GlaxoSmithKline group of companies. K.D. and S.G. declare no conflicts of interests.

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All authors participated in the design or implementation or analysis, and interpretation of the study; and the development of this manuscript. All authors had full access to the data and gave final approval before submission. All authors have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Trademark Statements

Rotarix is a registered trademark of GlaxoSmithKline group of companies. *Rotateq* is a trademark of Merck and Co., Inc.

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