Rotavirus Disease: Quantification of the Disease and its Impact due to Vaccination Using Electronic Claims Databases

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ABSTRACT OF THE DISSERTATION

ROTAVIRUS DISEASE: QUANTIFICATION OF THE DISEASE AND ITS IMPACT DUE TO VACCINATION USING ELECTRONIC CLAIMS DATABASES

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Estimates of the clinical and financial burden of RV disease among children aged less than 5 years before and after the introduction of the vaccines stratified by various age groups, particularly during recent years' RV seasons, are limited. Published studies to date using real-world practice data have included only the Rotateq vaccine, and have not included Medicaid low-income population[1]. Additionally, there is no published study that looked at the effectiveness of Rotarix in the US born infants. Hence this research addresses these limitations by quantifying the incidence and cost of Rotavirus (RV) and Acute Gastroenteritis (AGE) among children less than 5 years of age among commercial and Medicaid plans. Additionally the study also assessed the impact of incomplete and complete vaccination among those in commercial and Medicaid plans. Study population included beneficiaries who continuously received benefits for at least 6 months while aged <5 years were identified separately in commercial (2000-2010) and Medicaid (2002-2009) claims. Incidence of RV-coded encounters, diarrhea-coded but RV-attributable encounters, and first RV episodes were calculated, along with incremental cost of first RV episodes. Incidence rates among the post vaccination period reduced significantly compared to pre vaccination period for both RV coded and diarrhea coded, but RV attributable disease in both population. Incremental per-patient per-month cost of first RV episodes in Medicaid was $2,054 and $3608 in commercial. Forty two percent of children in

the commercial population had completed vaccination by 2010, and 11.1% of Medicaid patient had completed vaccination by 2009. Both complete and incomplete vaccination confers protection against RV episodes among inpatient visits, outpatient visits and ER visits for both population. Additionally there is evidence of strong indirect protection among those unvaccinated groups.

Acknowledgement

This work was funded by GlaxoSmithKline. I would like to thank researchers at Analysis group for their assistance in working with GSK and Truven to get me the analytical files necessary for the dataset.

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Overall Introduction

Rotavirus (RV) is the most common cause of severe gastroenteritis in infants and young children worldwide[2], and while rotavirus infects almost all children by age 5 years, severe, dehydrating gastroenteritis occurs primarily among children aged 3 to 35 months[3-7]. In the United States, rotavirus gastroenteritis results in approximately 410,000 physician visits, 205,000 to 272,000 emergency department visits, and 55,000 to 70,000 hospitalizations each year and direct and indirect costs of approximately $1 billion.[8-11] To further control the morbidity and mortality caused by this very common pediatric disease, vaccination against rotavirus is recognized as an important preventive strategy. The spectrum of rotavirus illness ranges from mild, watery diarrhea of limited duration to severe diarrhea with vomiting and fever that can result in dehydration with shock, electrolyte imbalance, and death.[12] Both the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics recommend routine immunization of infants with RV vaccine.[12;13] Two brands of oral RV vaccines are currently approved by the US Food and Drug Administration (FDA): Rotateq® (RV5) (Merck & Co., Whitehouse Station, NJ) and Rotarix® (RV1) (GlaxoSmithKline Biologicals, Rixensart, Belgium) . The vaccine is administered in 2 doses at 2 months and 4 months of age if Rotarix is used; and in 3 doses at 2 months, 4 months and 6 months of age if either Rotateq or a mix of brands (i.e., both Rotarix and Rotateq) is used. The percentage of children receiving the complete rotavirus vaccine series (either two or three immunizations, depending on the specific vaccine used) rose from 44% in 2009 to 59% in 2010[14]. Since the introduction of RV vaccines in 2006, the subsequent three RV seasons (i.e., 2007-2010) were consistently shorter and characterized by substantially fewer positive RV test results[15;16]. 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 <5 years of age including those age-ineligible to have received the vaccine, suggesting indirect benefits of vaccination[1;17-23]. However, few studies have assessed the burden of RV among children less than 5 years old in the low-income Medicaid population, particularly during the post-vaccine era. Also, few studies have quantified the economic burden of RV, particularly before vs. after the introduction of RV vaccines. Published studies to date using real-world practice data have included only the Rotateq vaccine, and have not included Medicaid low-income population. Additionally, there is no published study that looked at the effectiveness of Rotarix in the US born infants. The present study addresses these limitations by 1) Estimating the incidence of Acute Gastroenteritis (AGE) and Rotavirus (RV) among children aged less than 5 years using insurance claims data from commercial plans and Medicaid stratified by pre- and post-RV vaccines periods. 2)Estimating the cost of an RV episode per patient among children aged less than 5 years using insurance claims data from commercial plans and Medicaid stratified by pre- and post-RV vaccines periods. 3) Assessing the impact of partial and complete vaccination among those in commercial and Medicaid plans

Data Source

The study cohorts of interest were identified from the Truven Commercial for years 2000-2010 and the Truven Medicaid for years 2002-2009. Both databases contain actual payer costs, such that indirect costs and laboratory results are not available. A lag time of 6-9 months can be expected. Both databases are de-identified and in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 to preserve patient anonymity and confidentiality.

The Truven Commercial database contains claims from approximately 100 employers and a number of health plans. The database includes enrolment history, demographic variables, and claims for medical (provider and institutional) and outpatient pharmacy services. Inpatient services are at both the claim and summarized stay level. The database also includes the charges actually paid by the health plan, copay paid by the patient as well as total charges for these various medical and outpatient services. The database covers from 1996 to present and represents about 30 million covered lives consisting of employees and dependents from birth through 65 years of age. All census regions are represented, predominantly the South and North Central (Midwest) regions.

The Truven Medicaid contains the pooled healthcare experience of approximately 7 million Medicaid enrollees from multiple states. It includes inpatient services and prescription drug claims, as well as information on enrolment, long-term care, and other medical care. In addition to standard demographic variables such as age and gender, the database includes variables of particular value to researchers investigating Medicaid populations (such as ethnicity, maintenance assistance status, and Medicare eligibility).

Both Truven Commercial Claims and Medicaid databases have the following table structures:

Medical/surgical claims consisting of 4 tables:

a. Inpatient admission file: contains records that summarize hospitalization. The file contains information on principal procedure, principal diagnosis, and diagnosis related group (DRG). In addition to the principle procure and diagnosis codes, the admission record contain all diagnosis and procedures (upto 14 each). Finally to be

considered an admission, the grouping of these service records must meet certain criteria (eg: a room and board claim must be present).

b. Facility Header Table: contains information on header information facility claims. The facility Header Record ID identifier exists on both the Facility Header Table and the Inpatient Services and Outpatient Claims Tables to identify the individual service records that each header record comprises.

c. Inpatient File Service File: contains information on individual facility and professional encounters and services that the inpatient admission record comprises.

d. Outpatient Service Table: contains encounters and claims for services that were provided in doctor's office, hospital outpatient facility, emergency room or other outpatient facility.

- Aggregated Population Table: provides quarterly data on counts of covered lives for medical/surgical and outpatient pharmaceutical claims data for calculating rates.
- Outpatient Pharmaceutical Claims Table: Contains information on prescription drug claim

Annual Enrollment Summary and Detailed Table: Contains person level enrollment records with demographics (e.g., age, sex, region) and plan information (Health plan type, capitation, fee for service etc) for users and non-users of services contained in the Truven Commercial and Medicaid databases. The summary table contains single record per person per period of continuous enrollment and the detailed table contains one record per person per month of enrollment for an enrollee

The study received IRB approval from UMDNJ IRB body in February 2013.

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CHAPTER 1: Public health and cost burden of rotavirus infection among children less than 5 years of age.

Running Head: Burden of rotavirus disease

Keywords: rotavirus, diarrhea, cost, burden of illness, children,

ABSTRACT

Background: Few studies have assessed the burden of rotavirus (RV) among children aged <5 years before and after the introduction of the vaccine stratified by various age groups in commercial and in the low-income Medicaid population or quantified its economic burden.

Methods: Beneficiaries who continuously received benefits for at least 6 months while aged <5 years were identified separately in commercial (2000-2010) and Medicaid (2002-2009) claims. Eligible children were observed from their enrollment start date(s) to end of eligibility or 5 years old. Incidence of RV-coded encounters, diarrhea-coded but RV-attributable encounters, and first RV episodes were calculated, along with incremental cost of first RV episodes.

Results:, Incidence rates per 10,000 person-years of RV-coded among commercial population in the pre vs post vaccine introduction were for hospitalization was 16.67 (95%CI=16.19, 17.15) vs 5.58 (95%CI=5.37,5.80), outpatient visits was 13.20 (95%CI=12.78 , 13.63) vs 6.96 (95%CI=6.75, 7.20), and for ER visits was 11.26 (95%CI=10.87, 11.66) vs 4.85 (95%CI=4.66, 5.06). The Incidence rate for first RV episodes, 27.24 (95%CI=26.63, 27.86) vs 11.41 (95%CI=11.10, 11.72) per 10,000 person years. Incidence rates per 10,000 person-years of diarrhea coded rates commercial population in the pre and post vaccine introduction were 57.55 (95%CI=56.67,58.45) vs 36.17 (95%CI=35.63,36.73) for hospitalization, 1,496.06 (95%CI=1,491.48, 1,500.58) vs 1,436.58 (95%CI= 1,433.13, 1,440.04) for outpatient visits, and 203.88 (95%CI=202.20, 205.56) vs 194.76 (95%CI=193.49, 196.04) for ER visits. Incidence rates per 10,000 person-years of RV coded among Medicaid populations in the pre and post vaccine introduction were 19.78 (95%CI=19.14, 20.45) vs 10.53 (95%CI=9.60, 11.56) for hospitalizations, 19.39 (95%CI=18.75, 20.05) vs 11.72 (95%CI=10.73, 12.80) for outpatient visits and 27.61 (95%CI=26.84, 28.40) vs 9.11 (95%CI=8.24,10.07) for ER visits. Incidence rates per 10,000 person-years of diarrhea coded encounters among Medicaid populations in the pre and post vaccine introduction were 84.8 (95%CI=83.54, 86.27) vs 78.66 (95%CI=76.03, 81.39) for hospitalizations, 1788.37 (95%CI=1782.22, 1794.65) vs 1934.79

(95%CI=1921.56, 1948.11) for outpatient visits and 637.42 (95%CI=633.69,641.17) vs 555.34 (95%CI=548.27,562.5) for ER visits. Incremental per-patient per-month cost of first RV episodes in commercial was $3608 ((95%CI =3540, 3676) and Medicaid was $2,054 (95%CI=1997,2118).

Conclusions: The burden of both RV coded and diarrhea coded disease has decreased among children since the introduction of the vaccine among children less than 5 years of age who are insured by commercial or Medicaid plans.

INTRODUCTION

Rotavirus (RV) is the most common cause of severe diarrhea among children less than 5 years of age worldwide, accounting for greater than half a million deaths each year[24]. 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 years (2.7 million episodes annually), resulting annually in approximately 55,000 to70,000 hospitalizations, 410,000 outpatient visits, between 205,000 and 272,000 emergency room (ER) visits, and total annual direct and indirect costs of approximately $1 billion[8-11;25]. Previous studies have shown that RV occurred primarily among children aged 4-23 months, as well as during winter (vs. summer) months [11;26].

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[27]. By May 2007, vaccine coverage data reported that ~50% of infants aged three months had received at least 1 dose of RV5[28]. 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[12]. Both vaccines have demonstrated high efficacy (85%-98%) against severe RV disease in clinical trials [29;30].

Since the introduction of RV vaccines in 2006, the subsequent three RV seasons (i.e., 2007-2010) were consistently shorter and characterized by substantially fewer positive RV test results [15;16]. 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 years of age including those age-ineligible to have received the vaccine, suggesting indirect benefits of vaccination[1;17-23;31]. However, few studies have assessed the burden of RV among children less than 5 years old in the low-income Medicaid population, particularly during the post-vaccine era. This is particularly important in light of

low vaccination rates in this population. Also, few studies have quantified the economic burden of RV, particularly before vs. after the introduction of RV vaccines.

The present study used the Truven Commercial and Medicaid insurance claims databases to separately describe the clinical and economic burden of RV disease among children aged less than 5 years in each population, overall and stratified by age and pre/post-RV vaccine availability[32-35].

MATERIALS AND METHODS

Data Source

Data from the 2000-2010 Truven Commercial Claims and Encounters and the 2002-2009 Truven Medicaid databases were analyzed separately. 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, capitated or partially-capitated point-of-service, 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 years of age were captured. The Truven Medicaid database contained the pooled healthcare experience of approximately 28 million Medicaid enrollees from 11 geographically diverse states. Between 2002 and 2009, data from approximately 4.5 million children under 5 years of age were captured. In both databases, variables included patient demographics, date of service, place of service, ICD-9 codes, Current Procedural Terminology codes, length of hospital stay, and cost data in the form of payments made by insurers and patients to providers (physicians and hospitals).

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 months while aged less tha 5 years. Due to the absence of exact birth dates in Truven insurance claims data (only the birth year was available for HIPPA reasons), 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 as a population average. Beneficiaries who enrolled on or after 5 years of age, and those 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 months in duration were included in the analysis. 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 than1 year 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

A retrospective, longitudinal, open-cohort study design was used to evaluate the clinical burden of RV. 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 years of age, (imputed age based on year of birth) whichever occurred first. A matched-cohort design was used to evaluate economic burden of the first RV episode. RV patients were matched to 3 control non-RV patient to quantify the incremental costs attributable to first RV episodes. Control patients will be 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. Potential controls will have 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 will be imputed so that the duration from the eligibility start

date to the imputed index date is equal in duration from the eligibility start date to the index date of the matched RV episode. Potential controls also will have no RV claims from the imputed index date to 2 months following the imputed index date. Each matched control patient will be followed from its imputed index date to the earliest occurrence of: 2 months after the imputed index date, end of continuous eligibility (i.e., due to disenrollment, data cut-off, or death), or 5 years of age.

Study Outcomes

Clinical Burden

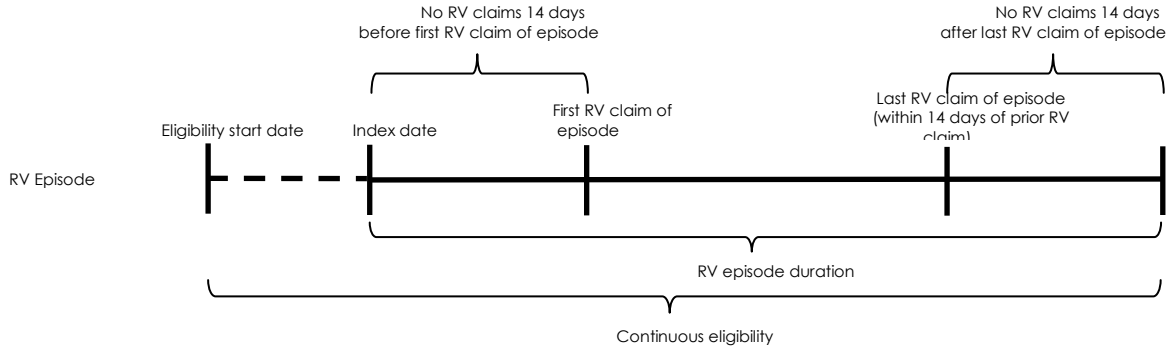
We described the clinical burden of RV by calculating the incidence rates of three events: RV-coded encounters (i.e., hospitalizations, outpatient visits, and ER visits), diarrhea-coded but attributable to RV encounters, and first episodes of RV infection. RV-coded encounters were identified by claims with the specific ICD-9 code for RV (008.61 - Enteritis due to rotavirus). An encounter identified a RV diagnosis as the primary discharge diagnosis or 1 of 15 non-primary discharge diagnoses in the inpatient-admission table was classified as a RV-related hospitalization. An encounter identified RV diagnosis in 1 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. An encounter was classified as 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 multiple encounters recorded in the database for the one RV episode.

However, since testing for RV is not performed routinely on all patients with diarrhea, claims coded as RV likely represent only a fraction of all RV-related encounters [10;24]. Thus, we also applied the previously used winter-summer residual excess (WRE) method to diarrhea-coded encounters to

estimate the proportion attributable to RV[32-35]. 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 months between November and April, and the summer-fall baseline between May and October. 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).

RV-coded claims dated within 14 days of each other were further used to identify an episode of RV infection. Each RV episode was assumed to last from 14 days before the first RV-coded claim of the episode to 14 days after the last RV-coded claim of the episode, unless truncated by start or end of continuous eligibility. Figure 1 illustrates how RV episodes were defined.

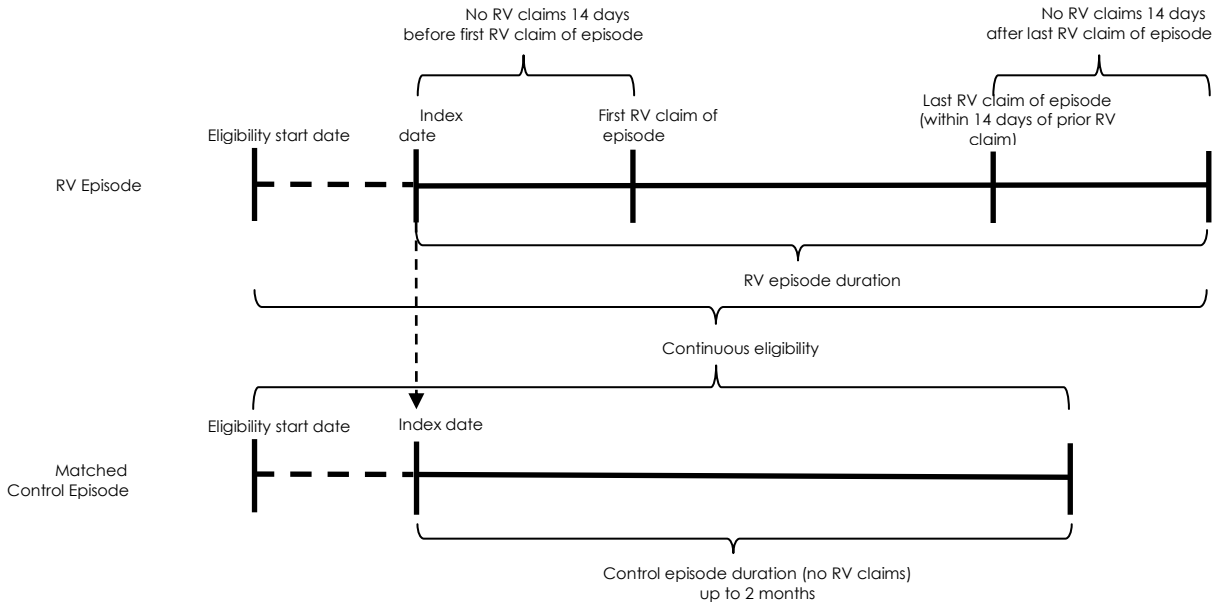
Figure 1: Study design scheme to identify RV episodes and their duration



Economic Burden

We assessed the incremental cost of RV episodes by calculating the per-patient per-month (PPPM) cost of first RV episodes and comparing them to the PPPM cost of matched non-RV control for the same duration of the RV episode. Controls were randomly selected from all eligible children with same year of birth, gender, and state of residence (for commercial population) or race (for Medicaid population) as the child with the RV episode. Control's duration of episodes were also required to include the calendar start date of the RV episode (imputed index date) and contain no RV claims from the imputed index date to two months thereafter. Each matched control was followed last from its imputed index date to the earliest of: two months after the imputed index date, end of continuous eligibility (due to disenrollment, data cut-off, or death), or 5 years of age (Figure 2). Each RV episode was matched to up to three controls.

Figure 2: Study design scheme to identify matched control episodes and their duration



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 commercial 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.

Clinical Burden

Incidence rates of RV-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. Incidence rates of diarrhea-coded but attributable to RV encounters, identified using the winter-summer residual excess (WRE) method, were similarly derived.

Economic Burden

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).

RESULTS

In the commercial population, a total of 3,998,708 eligible children were identified, 30% of whom were considered eligible from birth (Table 1-1). 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 1-1). 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) years.

The population characteristics results indicate that the two populations are rather different from each other, and hence must be cautioned against comparing the two population rates directly.

Clinical Burden

First RV Episodes

Overall incidence rates of first RV episodes were 17.34 (95%CI=17.04,17.64) per 10,000 person-years in the commercial population and 34.53 (95%CI=33.75,35.32) per 10,000 person-years in the Medicaid population (Table 1-2). In both populations, overall incidence rate decreased significantly after the introduction of RV vaccines, as did most age-specific rates except for among children 0-<2 months of age, where significant increases were observed. One possible explanation for this could be the heightened awareness and increased workups for RV infections among physicians since the introduction of the vaccine. The ICD-9 billing codes for RV infections hence may have included both the true- and false-positive cases. Consistent with the WRE method, the vast majority of RV episodes in the commercial and Medicaid populations occurred during the winter months of November to April (85.7% and 89.9%, respectively).

RV-Coded Encounters

Eligible children less than 5 years of age in the commercial population were observed for a total of 7,405,228 person-years over the years 2000-2010. During this time, a total of 20,796 RV-coded encounters were recorded. Table 1-3 summarizes the resulting incidence rates per 10,000 person-years, which 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. Incidence of RV-coded hospitalizations and ER visits peaked at 1 to <2 years old at 19.04 (95%CI=18.36, 19.75) and 14.20 (95%CI=13.61, 14.81) per 10,000 person-years, respectively. Incidence of RV-coded outpatient visits peaked at 10 to <12 months old at 22.86 (95%CI =20.65, 25.30) per 10,000 person-years.

In the Medicaid population, eligible children less than 5 years of age were observed for a total of 2,172,990 person-years over 2002-2009. During this time, a total of 13,302 RV-coded encounters were recorded. Summarized in Table 3, the resulting incidence rates per 10,000 person-years were at 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. Incidence of RV-coded hospitalizations, outpatient visits, and ER visits peaked at 6 to less than12 months old at 37.95 (95%CI: 35.48, 40.59), 43.13 (95%CI: 40.49 - 45.94) and 59.07 (95%CI: 55.97-32.34) per 10,000 person-years, respectively.

As shown in Table 3, incidence rates for children less than5 years old in the commercial population declined by 67% (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% (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% (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. The corresponding percentage declines in the Medicaid population were 47% (19.78 (95%CI: 19.14,10.53) to 10.53 (95%CI: 9.60,11.56) per 10,000 person-years) for hospitalizations, 40% (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% (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-specific rates between the pre and the post vaccination periods.

In the commercial population, among both hospitalization rate and ER rate, the largest decline between the pre and post vaccination period for RV coded events was among those < 1 year old (73.1% ((Incidence rates per 10,000 during pre and Post vaccination period (23.39 (95%CI=21.93, 24.94) and 6.17 (95%CI=5.61, 6.78))) and 65.8% (15.73 (95%CI=14.54, 17.01) and 5.37 (95%CI=4.85,5.94))respectively) and smallest decline among those 2-5 year olds (53.5% (7.23 (95%CI=6.83,7.64) and 3.36 (95%CI=3.16 ,3.58)) and 36.6% (4.69 (95%CI=4.38 ,5.03) and 2.97 (95%CI=2.78 ,3.18))respectively).

In the Medicaid population, among both hospitalization rate and ER rate, the largest decline between the two periods was among those less than 1 year old (58% (Incidence rates per 10,000 during pre and Post vaccination period (36.42 (95%CI=34.45 ,38.50) and 15.17 (95%CI=13.07,17.62)))) and 75% 55.55 (95%CI=53.11, 58.11) and 13.50 (95%CI=11.52, 15.81) respectively) and smallest decline among

those 2-5 year olds (26% (6.65 (95%CI=6.17,7.17) 4.92 (95%CI=4.07, 5.95)and 51% 8.93 (95%CI=8.37, 9.53) 4.32 (95%CI=3.53,5.29)respectively). The data here is consistent with the type of resources Medicaid patients tend to use. Medicaid patients are less likely to have a medical home and tend to use more ER services for their Medical need and as such with the introduction of the vaccine the largest decrease is seen at ER vs hospitalization.

RV coded Encounters by calendar year

Figure 3 shows the rates of resource utilization across the calendar years 2000-2010. The figure shows that 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 2006-2007 season, and the steepest decline for hospitalization, ER and outpatient visits was in 2009-2010 season. The 2008-2009 seasons did experience an increase in resource utilization in for all points of care (33%-37%). This is consistent with the research that has shown a pattern of biennial increase in RV activity even after the introduction of the vaccines.[36]

Correspondingly for Medicaid patients the decline began in 2006-2007 season and this season had the steepest decline for ER, hospitalization and outpatient visits. The 2008-2009 seasons in this population also saw an increase in resource utilization for all points of care (29%-35%). This is consistent with the research that has shown a pattern of biennial increase in RV activity even after the introduction of the vaccines.[36]

Diarrhea-Coded Encounters

Among those less than 5 years of age, between 2000-2010 the rate of diarrhea coded hospitalization, outpatient visits and ER visit was 44.19 (95%CI=43.71,44.67), 1,458.87 ((95%CI=1,456.12, 1,461.62) and 198.18 ((95%CI=197.17,199.20)per 10,000 person years respectively (Table 4). All three points of care saw slight, yet statistically significant overall reduction in the rates per 10,000 person years between the pre and post vaccine introduction period among commercial population: 33.6% (57.5

(95%CI= 56.76, 58.45) vs 36.17 (95%CI=35.63, 36.73)) for hospitalization, 4.0% (1,458.87 ((95%CI=1,456.12, 1,461.62) vs 1436.58 (95%CI=1,433.13, 1440.04)) for outpatient visits, and 4.5% (203.88 (95%CI= 202.20,205.56) vs 194.76 (95%CI=193.49, 196.04)) for ER visits.

Correspondingly among those in Medicaid population among those less than 5 years of age, between 2002-2009 the rate of hospitalization, outpatient visits and ER visit was 83.68, 1,818 and 621 per 10,000 person-years respectively. The rate per 10,000 person years of hospitalization and ER visits experienced a slight, yet statistically significant overall reduction between the pre and post vaccine introduction period: 7% (84.8 (95%CI=83.54, 86.27) vs 78.66 (95%CI=76.03, 81.39)) for hospitalization and 12 % (637.42 (95%CI=633.69, 641.17) vs 555.34 (95%CI=548.27, 562.5)) for ER visits. The outpatient visits that were diarrhea related increased by 8% (1788 (95%CI=1782.22, 1793.74) vs 1934.79 (95%CI=1,921.56, 1948.11) between the pre and post vaccination periods.

Diarrhea-Coded but Attributable to RV Encounters

In both populations, incidence rates of diarrhea-coded hospitalizations, outpatient visits, and ER visits were higher during the winter months of November to April than during the summer months of May to October. Table 5 summarizes the number of diarrhea-coded hospitalizations, outpatient visits, and ER visits according to season and the resulting estimate for the number of RV-attributable encounters according to the WRE method. Overall in the commercial and Medicaid populations, RV accounted for 39% and 37% of all diarrhea-coded hospitalizations, 16% and 19% of all diarrhea-coded outpatient visits, and 30% and 27% of all diarrhea-coded ER visits among children less than5 years of age, respectively. These proportions in the commercial and Medicaid populations translated to RV-attributable hospitalization rates of 17.99 and 31.14, outpatient visit rates of 230.33 and 350.48, and ER visit rates of 60.25 and 168.25 per 10,000 person-years, respectively. The proportions of diarrhea-coded encounters attributable to RV and their resulting RV-attributable incidence rates decreased following RV vaccine availability.

Economic Burden

First RV Episodes

Table 6 describes the PPPM cost differences between first RV episodes and their matched control episodes. Overall, without comparing pre- post-vaccination differences first RV episodes in the commercial population were significantly more expensive than similar episodes without RV by $3,608 (95% CI: $3,540,$3,676) PPPM. The corresponding PPPM cost difference in the Medicaid population, while also significant, was more than a thousand dollars lower at $2,054 (95% CI: $1,997-$2,118). Most of the PPPM cost differences were due to differences in hospitalization costs.

In the commercial population, first RV episodes that occurred after the introduction of RV vaccines were significantly cheaper than those that occurred before RV vaccines. When stratified by age groups, first RV episodes were cheaper after the introduction of RV vaccines among children aged less than1 year but not older. In the Medicaid population, the introduction of RV vaccines did not seem to impact the cost of first RV episodes; all episodes were approximately $2,000 PPPM more expensive than matched control episodes. When stratified by age groups, RV episodes after the introduction of RV vaccines were sometimes cheaper (i.e., 2-<4 months of age) and sometimes more expensive (i.e., 4-<6 months of age) than before RV vaccines.

Given that the cost data are skewed, sensitivity analysis was performed using an adjusted (controlling for gender, race, and insurance plan type) two part model. Table 7 compares the results for the overall PPPM cost using the adjusted two part model and the unadjusted linear cost model described in table 6. The overall PPPM incremental cost of an RV episode from an adjusted two part model and unadjusted linear model among commercial population is $3615 (95%CI: $3556, $3696) and $3,608 (95% CI: $3,540,$3,676). Correspondingly the incremental PPPM costs in Medicaid population from an adjusted two part model and unadjusted linear model is $2,106 (95%CI: $2041, $2182) and

$2,054 (95% CI: $1,997-$2,118). Hence the results generated using a linear model and the adjusted two part model are very similar.

DISCUSSION

Findings from the present analysis of RV burden among two differently insured populations, one by commercial private insurance and one by Medicaid, suggest that the clinical burden of RV diseases among children less than 5 years of age has reduced since 2005-2006 season. This trend was observed in all three outcomes of RV burden, namely incidence rates of RV-coded encounters, diarrhea-coded encounters attributable to RV using the WRE method, and episodes of first RV infection. In addition as reported in previous studies, this study also noted that the disease burden did increase in the 2008-2009 due to the biennial increase in RV activity even after the introduction of the vaccines. [20] In both populations, the clinical burden of RV appeared to be highest among children less than 2 years of age.

In both the commercial and Medicaid populations, PPPM costs of first RV episodes were consistently higher than for matched control for hospitalizations, outpatient visits, ER visits and pharmacy. Compared with the pre-vaccination period, the difference in total cost between an RV and control episode during the post-vaccination period was slightly lower (Post vaccine incremental total cost was3,399 (95% CI: 3296,3511) vs pre vaccine incremental total cost 3754 (95%CI: 3672,3819)) in the commercial population; in the Medicaid population (post vaccine incremental total cost 2291 (95%CI: 2085,2501) vs pre vaccine incremental total cost 2022 (95%CI: 1963,2090). Cortese[1] reported that nationally for 2007-2009 periods one would expect to save approximately 278 million in treatment cost.

The present study findings also confirmed other reports of a decline in RV activity in the US after the introduction of RV vaccine[1;17-23;31]. In the current study, in both populations, the incidence of RV-

coded encounters among children less than 5 years of age declined after the introduction of RV vaccines. In the commercial population, incidence 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[1] in analysis of the commercial data. 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 that study. 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. The incidence of diarrhea-coded but attributable to RV encounters likewise declined in both populations. Cortes et al.[1] reported declines in diarrhea-associated hospitalization rates in the commercial 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 commercial and Medicaid populations by 38% and 7%, respectively, for the post- vs. pre-vaccination periods. Our study found modest reductions in the diarrhea-associated ER visit rates for the post- vs. pre-vaccination periods and slightly more outpatient visits in Medicaid population. Cortes et al.[1] reported similar modest reduction in the ER visit rate and higher outpatient visit rates for some age groups in the post- vs. pre-vaccination periods.

Some limitations of the present study should be considered. First, as this was intended to be a descriptive study, we did not assess population RV vaccine coverage and correlate it with declines in RV burden after vaccines were introduced. As such, the study solely described the burden of RV among children aged less than5 years in the two insured populations before and after RV vaccine availability, overall and within specific age groups. Second, 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. Third, although we conducted stratified analysis by age and pre/post-RV vaccine availability, we may not have accounted

for all confounders. Fourth, we examined data from only two and three post-vaccine RV seasons in commercial (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. Fifth, 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. 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. Finally, for children who enrolled after birth, the first RV episode captured in the claims data may not actually be the first RV episode experienced.

CONCLUSIONS

Findings from the present claims database analysis suggest that the clinical burden of RV disease has reduced in both commercial and Medicaid population since the introduction of the vaccines in 2006. The overall reduction in first RV episode, among commercial and Medicaid population since the introduction of the vaccine was 58% and 43% respectively. Average attributable PPPM episode cost of RV was approximately $3,600 among commercially-insured and $2,000 among Medicaid-insured children.

ACKNOWLEDGEMENTS AND CONFLICT OF INTEREST

TABLES

Table 1 - 1: Baseline characteristics of eligible children less than 5 years old

Characteristic	Commercial N=3,998,708	Medicaid N=1,034,440
Eligible from birth[1], n (%)	1,191,474 (29.8)	504,098 (48.7)
Age at first continuous eligibility start, years		
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 continuous eligibility start, 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, years		
Mean ± SD	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.

1. Children born in the year that their eligibility first started were assumed to be eligible from birth. For these children, their birth date was assumed to be their eligibility start date. For the remaining children, their birth date was assumed to be June 30th of their birth year.

Table 1-2: Incidence rates of first RV episodes in commercial and Medicaid populations, overall and stratified by age and pre/post-RV vaccine availability

	Incidence rate per 10,000 person-years[2] (95% CI)	
	Commercial	**Medicaid**
Overall	17.34 (17.04 - 17.64)	34.53 (33.75 - 35.32)
Pre[3]	27.24 (26.63 - 27.86)	37.71 (36.81 - 38.63)
Post[3]	11.41 (11.10 - 11.72)*	21.27 (19.92 - 22.72)*
Age		
<1 year[4]	30.39 (29.37 - 31.45)	68.59 (66.22 - 71.04)
Pre[3]	44.76 (42.72 - 46.89)	78.46 (75.54 - 81.49)
Post[3]	22.10 (21.02 - 23.24)*	38.94 (35.47 - 42.75)*
0-<2 months[4]	37.74 (35.09 - 40.59)	52.34 (47.40 - 57.78)
Pre[3]	23.61 (20.42 - 27.29)	41.62 (36.71 - 47.20)
Post[3]	47.31 (43.49 - 51.47)*	90.19 (76.82 - 105.90)*
2-<4 months[4]	21.57 (19.58 - 23.76)	52.83 (47.93 - 58.24)
Pre[3]	25.51 (22.11 - 29.45)	59.16 (53.24 - 65.75)
Post[3]	19.11 (16.76 - 21.78)*	32.71 (25.39 - 42.12)*
4-<6 months[4]	22.55 (20.52 - 24.78)	61.18 (55.96 - 66.89)
Pre[3]	35.55 (31.40 - 40.26)	73.54 (66.92 - 80.81)
Post[3]	15.08 (13.06 - 17.43)*	25.25 (19.19 - 33.22)*
6-<12 months[4]	33.38 (31.83 - 35.01)	80.88 (77.23 - 84.70)
Pre[3]	65.05 (61.38 - 68.93)	98.84 (94.15 - 103.76)
Post[3]	16.70 (15.37 - 18.15)*	30.07 (25.93 - 34.88)*
1-<2 years	30.37 (29.50 - 31.26)	57.74 (55.52 - 60.04)
Pre[3]	50.39 (48.57 - 52.27)	64.56 (61.94 - 67.28)
Post[3]	18.28 (17.43 - 19.16)*	29.87 (26.42 - 33.77)*
2-<5 years	7.52 (7.28 - 7.78)	11.22 (10.64 - 11.83)
Pre[3]	10.90 (10.41 - 11.41)	11.90 (11.24 - 12.59)
Post[3]	5.52 (5.26 - 5.80)*	8.02 (6.91 - 9.31)*

Notes:

CI = confidence interval; RV = rotavirus.

1. ICD-9 code 008.61 (Enteritis due to rotavirus) was used to identify RV episodes.

2. Incidence rates were calculated by dividing the number of RV episodes by the person-years of follow-up. Person-years for first RV episodes include all continuous eligibility periods before first RV episode start date for patients who experienced at least one RV episode and all continuous eligibility periods for patients who experienced no RV episode. Poisson regressions were used to generate the incidence rates' 95% CIs.

3. Pre- and post-RV vaccine availability periods were defined as the time through January 1, 2007 and the time after that date, respectively.

4. Calculated among children less than 5 years old eligible from birth.

5. * $p<0.05$ between pre and post vaccination rates.

Table 1-3: Incidence rates of RV-coded hospitalizations, outpatient visits, and ER visits in commercial and Medicaid populations, overall and stratified by age and pre/post-RV vaccine availability1

	Incidence rate per 10,000 person-years[2] (95% CI)					
	Commercial			Medicaid		
	Hospitalizations	Outpatient Visits	ER Visits	Hospitalizations	Outpatient Visits	ER Visits
Overall, < 5 years	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[3]	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[3]	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 year[4]	12.47 (11.82 - 13.15)	14.12 (13.43 - 14.85)	9.16 (8.61 - 9.75)	31.12 (29.53 - 32.78)	34.00 (32.35 - 35.74)	45.05 (43.14 - 47.05)
Pre[3]	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[3]	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-<2 months[4]	6.51 (5.46 - 7.76)	6.35 (5.31 - 7.59)	4.57 (3.70 - 5.63)	18.71 (15.84 - 22.09)	16.15 (13.50 - 19.31)	19.38 (16.46 - 22.82)
Pre[3]	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[3]	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-<4 months[4]	6.98 (5.89 - 8.27)	9.28 (8.01 - 10.76)	5.30 (4.36 - 6.44)	26.98 (23.54 - 30.92)	25.28 (21.97 - 29.10)	34.80 (30.87 - 39.23)
Pre[3]	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[3]	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-<6 months[4]	9.83 (8.53 - 11.34)	12.23 (10.76 - 13.89)	6.97 (5.89 - 8.26)	27.43 (24.01 - 31.34)	33.37 (29.58 - 37.65)	39.44 (35.30 - 44.07)
Pre[3]	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[3]	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-<12	17.74	19.54	13.14	37.95	43.13	59.07

months[4]	(16.62 - 18.93)	(18.36 - 20.79)	(12.18 - 14.17)	(35.48 - 40.59)	(40.49 - 45.94)	(55.97 - 62.34)
Pre[3]	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[3]	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-<2 years	19.04 (18.36 - 19.75)	16.70 (16.06 - 17.36)	14.20 (13.61 - 14.81)	33.31 (31.64 - 35.06)	30.43 (28.84 - 32.11)	42.55 (40.66 - 44.53)
Pre[3]	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[3]	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-<5 years	4.80 (4.61 - 5.01)	4.14 (3.95 - 4.33)	3.61 (3.44 - 3.79)	6.35 (5.92 - 6.81)	6.21 (5.78 - 6.66)	8.12 (7.63 - 8.64)
Pre[3]	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[3]	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. ICD-9 code 008.61 (Enteritis due to rotavirus) was used to identify RV-coded encounters.

2. Incidence rates were calculated by dividing the number of RV-coded encounters by the person-years of follow-up. Poisson regressions were used to generate the incidence rates' 95% CIs.

3. Pre- and post-RV vaccine availability periods were defined as the time through January 1, 2007 and the time after that date, respectively.

4. Calculated among children less than 5 years old eligible from birth.

5. * $p<0.05$ between pre and post vaccination rates.

Table 1- 4: Incidence rates of diarrhea-related hospitalizations, outpatient visits, and ER visits in Truven Commercial and Medicaid, overall and stratified by age (pre and post-RV vaccines)

	Incidence rate per 10,000 person-years[2] (95% CI)					
	Commercial			Medicaid		
	Hospitalizations	Outpatient Visits	ER Visits	Hospitalizations	Outpatient Visits	ER Visits
Overall, < 5 years	44.19 (43.71 - 44.67)	1,458.87 (1,456.12 - 1,461.62)	198.18 (197.17- 199.20)	83.68 (82.47 - 84.91)	1,816.78 (1,811.12 - 1,822.45)	621.4 (618.19 - 624.82)
Pre[3]	57.55 (56.67 - 58.45)	1,496.03 (1,491.48 - 1,500.58)	203.88 (202.20 - 205.56)	84.8 (83.54 - 86.27)	1,788.37 (1,782.12 - 1,794.65)	637.42 (633.69 - 641.17)
Post[3]	36.17 (35.63 - 36.73)*	1,436.58 (1,433.13 - 1,440.04)*	194.76 (193.49 - 196.04)*	78.66 (76.03 - 81.39)*	1,934.79 (1,921.56 - 1,948.11)*	555.34 (548.27 - 562.50)*
Age						
<1 year[4]	70.79 (69.22 - 72.39)	2,260.95 (2,252.02 - 2,269.92)	281.62 (278.48 - 284.80)	154.87 (151.29- 158.53)	2,819.83 (2,804.43 - 2,835.32)	984.46 (975.37 - 993.63)
Pre[3]	89.92 (87.01 - 92.92)	2,407.37 (2,392.15 - 2,422.68)	294.04 (288.76 - 299.43)	160.44 (156.24 164.75)	2,870.74 (2,852.81 - 2,888.79)	1,041.5 (1,030.72- 1,052.39)
Post[3]	59.75 (57.95 - 61.60)*	2,176.44 (2,165.44 - 2,187.49)*	274.45 (270.56 - 278.39*	138.14 (131.4 - 145.16)*	2,666.83 (2,636.94 - 2,697.06)*	812.99 (796.56 - 829.76)*
0-<2 months[4]	79.87 (75.96 - 83.99)	1,385.61 (1,369.00 - 1,402.43)	178.95 (173.05 - 185.06)	176.71 (167.40 - 186.53)	1,753.61 (1,723.76 - 1,783.98)	619.89 (602.24 - 638.05)
Pre[3]	84.65 (78.39 - 91.41)	1,540.03 (1,512.55 - 1,568.02)	184.12 (174.77 - 193.96)	171.79 (161.44 - 182.81)	1,766.97 (1,733.07 - 1,801.54)	635.72 (615.52 - 656.59)
Post[3]	76.64 (71.72 - 81.91)	1,281.11 (1,260.47 - 1,302.09)*	175.46 (167.93 - 183.33)	194.07 (173.87 - 216.62)	1,706.36 (1,644.27 - 1,770.79)	563.90 (528.69 - 601.46)*
2-<4 months[4]	60.37 (56.98 - 63.96)	1,948.67 (1,928.96 - 1,968.59)	215.98 (209.48 - 222.68)	164.35 (155.52 - 173.67)	2,566.87 (2,531.27 - 2,602.97)	846.63 (826.29 - 867.47)
Pre[3]	65.29 (59.70 - 71.41)	2,058.03 (2,025.46 - 2,091.12)	211.42 (201.15 - 222.21)	166.69 (156.54 - 177.50)	2,628.99 (2,587.73 - 2,670.92)	899.06 (875.06 - 923.72)
Post[3]	57.29 (53.11 - 61.78)	1,880.28 (1,855.63 - 1,905.26)*	218.83 (210.52 - 227.46)	156.90 (139.79 - 176.11)	2,369.32 (2,299.94 - 2,440.79)*	679.90 (643.21 - 718.69)*
4-<6 months[4]	57.23 (53.94 - 60.71)	2,141.06 (2,120.48 - 2,161.85)	254.91 (247.87 - 262.15)	139.44 (131.45 - 147.91)	2,737.52 (2,701.30 - 2,774.23)	960.63 (939.27 - 982.47)
Pre[3]	73.72 (67.63 - 80.35)	2,261.27 (2,226.35 - 2,296.74)	261.50 (249.80 - 273.75)	148.10 (138.59 - 158.27)	2,834.50 (2,791.82 - 2,877.83)	1,021.60 (996.11 - 1,047.75)
Post[3]	47.75 (44.03 - 51.79)*	2,072.01 (2,046.63 - 2,097.70)*	251.13 (242.39 - 260.18)	114.21 (100.39 - 129.93)*	2,455.24 (2,387.90 - 2,524.49)*	783.15 (745.51 - 822.68)*
6-<12 months[4]	76.39 (74.03 - 78.83)	2,749.20 (2,734.86 - 2,763.62)	354.47 (349.35 - 359.67)	149.83 (144.85 - 154.99)	3,289.27 (3,265.60 - 3,313.11)	1,161.0 (1,147.00 - 1,175.22)
Pre[3]	108.89 (104.13 - 113.88)	2,988.86 (2,963.46 - 3,014.48)	389.27 (380.17 - 398.58)	158.64 (152.69 - 164.83)	3,354.91 (3,327.13 - 3,382.93)	1,240.72 (1,223.87 - 1,257.80)
Post[3]	59.24 (56.69 - 61.91)*	2,622.77 (2,605.46 - 2,640.18)*	336.12 (329.96 - 342.39)*	124.85 (116.10 - 134.25)*	3,103.17 (3,058.32 - 3,148.68)*	935.06 (910.59 - 960.20)*
1-<2 years	69.90 (68.58 -	2,309.56 (2,301.89 -	306.06 (303.28 -	117.43 (114.26 -	2,598.18 (2,583.12 -	879.03 (870.30 -

	71.25)	2,317.25)	308.87)	120.68)	2,613.31)	887.86)
Pre[3]	94.09 (91.60 - 96.64)	2,351.68 (2,339.10 - 2,364.33)	320.10 (315.48 - 324.78)	122.53 (118.93 - 126.24)	2,555.51 (2,538.87 - 2,572.26)	909.70 (899.79 - 919.72)
Post[3]	55.25 (53.76 - 56.77)*	2,284.05 (2,274.39 - 2,293.74)*	297.56 (294.09 - 301.07)*	96.53 (90.19 - 103.33)*	2,772.88 (2,737.90 - 2,808.30)*	753.44 (735.31 - 772.01)*
2-<5 years	26.21 (25.75 - 26.69)	914.36 (911.59 - 917.14)	132.09 (131.03 - 133.14)	41.78 (40.65 - 42.93)	1,126.80 (1,120.89 - 1,132.73)	378.81 (375.39 - 382.26)
Pre[3]	32.28 (31.43 - 33.14)	889.80 (885.32 - 894.30)	128.14 (126.45 - 129.86)	42.15 (40.91 - 43.43)	1,105.81 (1,099.37 - 1,112.29)	387.56 (383.76 - 391.41)
Post[3]	22.62 (22.07 - 23.17)*	928.93 (925.41 - 932.47)*	134.43 (133.09 - 135.78)*	40.01 (37.44 - 42.76)	1,225.03 (1,210.40 - 1,239.83)*	337.81 (330.18 - 345.63)*

CI = confidence interval; RV = rotavirus; ER = emergency room.

1. ICD-9 codes 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), 006.0-007.9 (excluding 006.3-006.6) (Parasitic gastroenteritis) were used to identify diarrhea-related visits.
2. Incidence rates were calculated by dividing the number of diarrhea-related visits by the person-years of follow-up. Poisson regressions were used to generate the incidence rates' 95% CIs.
3. Pre- and post-RV vaccines were defined as before and on/after 01/01/2007, respectively
4. Calculated among children less than 5 years old eligible from birth.
5. * $p<0.05$ between pre and post vaccination rates.

Table 1 -5:Estimates from the winter residual excess (WRE) method of diarrhea-coded encounters attributable to RV for hospitalizations, outpatient visits, and ER visits in commercial and Medicaid populations, overall and stratified by pre/post-RV vaccine availability

	Person-Years of Observation [A]	Winter Diarrhea-Coded Encounters[1],[2] [B]	Summer Diarrhea-Coded Encounters[2] [C]	Diarrhea-Coded Encounters Per 10,000 Person-Years ([B]+[C])/([A]/10000)	RV-Attributable Diarrhea-Coded Encounters (Estimate)[3] [B] - [C]	Proportion of Diarrhea-Coded Encounters Attributable to RV, % ([B]-[C])/([B]+[C])	RV-Attributable Diarrhea-Coded Encounters Per 10,000 Person-Years ([B]-[C])/([A]/10000)
Commercial							
Hospitalizations							
Overall	7,405,228	22,747	9,977	44.19	12,770	39.0%	17.24
Pre[4]	2,776,690	11,894	4,087	57.55	7,807	48.9%	28.12
Post[4]	4,628,538	10,853	5,890	36.17	4,963	29.6%	10.72
Outpatient visits							
Overall	7,405,228	626,768	456,201	1462.44	170,567	15.7%	230.33
Pre[4]	2,776,690	251,899	163,609	1496.41	88,290	21.2%	317.97
Post[4]	4,628,538	374,869	292,592	1442.06	82,277	12.3%	177.76
ER visits							
Overall	7,405,228	95,688	51,068	198.18	44,620	30.4%	60.25
Pre[4]	2,776,690	39,242	17,368	203.88	21,874	38.6%	78.78
Post[4]	4,628,538	56,446	33,700	194.76	22,746	25.2%	49.14
Medicaid							
Hospitalizations							
Overall	2,172,990	12,475	5,709	83.68	6,766	37.2%	31.14
Pre[4]	1,751,445	10,495	4,373	84.89	6,122	41.2%	34.95
Post[4]	421,545	1,980	1,336	78.66	644	19.4%	15.28
Outpatient visits							
Overall	2,172,990	235,694	159,534	1818.82	76,160	19.3%	350.48
Pre[4]	1,751,445	189,516	123,724	1788.47	65,792	21.0%	375.64
Post[4]	421,545	46,178	35,810	1944.94	10,368	12.6%	245.95
ER visits							
Overall	2,172,	85,805	49,245	621.49	36,560	27.1%	168.25

Pre[4]	1,751,990	72,170	39,470	637.42	32,700	29.3%	186.70
Post[4]	421,545	13,635	9,775	555.34	3,860	16.5%	91.57

Notes:

RV = rotavirus; ER = emergency room.

1. ICD-9 codes 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), 006.0-007.9 (excluding 006.3-006.6) (Parasitic gastroenteritis) were used to identify diarrhea-coded encounters.

2. Winter months were defined as November through April. Summer months were defined as May through October.

3. Determined by using the WRE method, as described in the Methods section.

4. Pre- and post-RV vaccine availability periods were defined as the time through January 1, 2007 and the time after that date, respectively.

Figure 3: Incidence rate of RV related hospitalization, outpatient visits and ER visits in Truven Commercial and Medicaid by calendar year

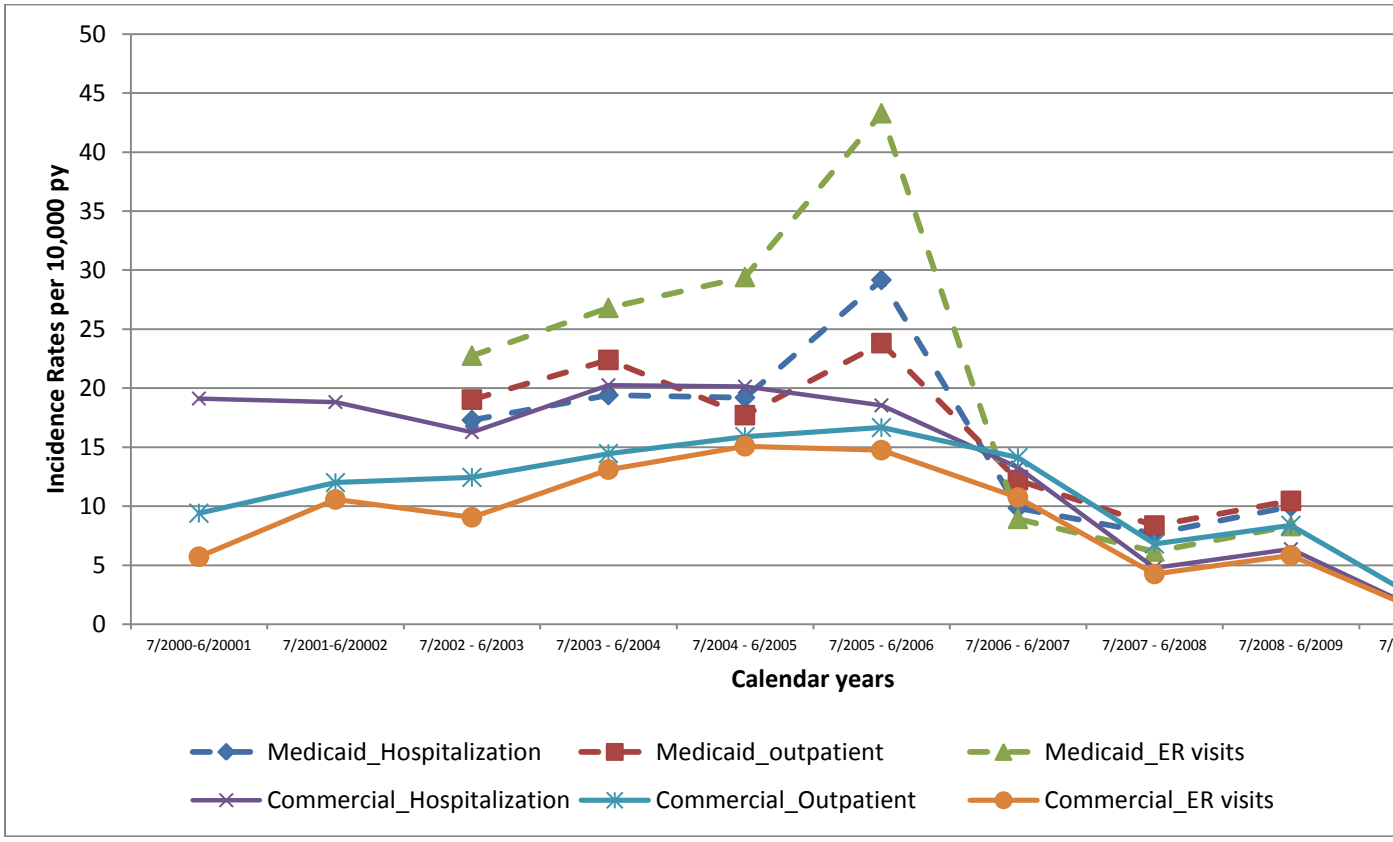


Table 1 -6:PPPM cost differences of first RV episodes and their matched control episodes in commercial and Medicaid populations, overall and stratified by age and pre/post-RV vaccine availability

	PPPM Cost Differences (Incremental Cost of RV Episodes)[1]			
	Commercial		Medicaid	
	Mean	(95% CI)	Mean	(95% CI)
Overall	$3,608	($3,540 - $3,676)	$2,054	($1,997 - $2,118)
Hospitalizations	$2,695	($2,631 - $2,756)	$1,529	($1,477 - $1,587)
Outpatient visits	$589	($566 - $616)	$293	($273 - $315)
ER visits	$294	($280 - $309)	$158	($150 - $168)
Pharmacy	$30	($25 - $34)	$74	($65 - $84)
Pre[2]	$3,754	($3,672 - $3,819)	$2,022	($1,963 - $2,090)
Hospitalizations	$2,865	($2,792 - $2,935)	$1,495	($1,440 - $1,555)
Outpatient visits	$561	($530 - $589)	$284	($265 - $306)
ER visits	$295	($277 - $314)	$168	($157 - $178)
Pharmacy	$33	($28 - $37)	$76	($66 - $86)
Post[2]	$3,399	($3,296 - $3,511)*	$2,291	($2,085 - $2,504)
Hospitalizations	$2,451 *	($2,363 - $2,540)	$1,784 *	($1,614 - $1,976)
Outpatient visits	$629	($588 - $676) *	$363	($277 - $463)
ER visits	$293	($273 - $314)	$87	($74 - $101) *
Pharmacy	$25	($16 - $34)	$56	($38 - $79)
Age				
< 1 year[3]	$2,955	($2,804 - $3,097)	$1,970	($1,865 - $2,058)
Pre[2]	$3,682	($3,496 - $3,871)	$1,964	($1,870 - $2,066)
Post[2]	$2,105 *	($1,918 - $2,298)	$2,008	($1,739 - $2,319)
0 - < 2 months[3]	$1,659	($1,365 - $1,932)	$2,191	($1,845 - $2,539)
Pre[2]	$3,425	($2,740 - $4,200)	$2,707	($2,275 - $3,160)
Post[2]	$1,083	($762 - $1,395) *	$1,367	($960 - $1,895) *
2 - < 4 months[3]	$2,309	($1,980 - $2,642)	$2,032	($1,772 - $2,269)
Pre[2]	$3,272	($2,703 - $3,951)	$2,075	($1,773 - $2,380)
Post[2]	$1,536 *	($1,231 - $1,883)	$1,800	($1,231 - $2,490)
4 - < 6 months[3]	$3,315	($2,951 - $3,742)	$2,289	($1,998 - $2,621)
Pre[2]	$4,253	($3,717 - $4,855)	$2,142	($1,889 - $2,430)
Post[2]	$2,021 *	($1,581 - $2,470)	$3,567 *	($2,453 - $5,084)
6 - < 12 months[3]	$3,572	($3,381 - $3,745)	$1,824	($1,724 - $1,937)
Pre[2]	$3,663	($3,443 - $3,877)	$1,787	($1,679 - $1,910)
Post[2]	$3,381	($3,062 - $3,706)	$2,175	($1,702 - $2,690)
1 - < 2 years	$3,861	($3,760 - $3,972)	$2,066	($1,973 - $2,181)
Pre[2]	$3,847	($3,720 - $3,964)	$2,010	($1,916 - $2,123)
Post[2]	$3,884	($3,703 - $4,059)	$2,576 *	($2,194 - $3,024)
2 - < 5 years	$3,981	($3,861 - $4,092)	$2,116	($1,974 - $2,250)
Pre[2]	$3,772	($3,638 - $3,914)	$2,042	($1,897 - $2,193)
Post[2]	$4,227 *	($4,056 - $4,403)	$2,637	($2,158 - $3,186)

Notes:

CI = confidence interval; PPPM = per-patient per-month; RV = rotavirus; SD = standard deviation. Costs are in 2010 USD.

1. The p-value and CI of PPPM cost differences between RV episodes and matched control episodes were calculated using the non-parametric bootstrapping method.

2. Pre- and post-RV vaccine availability periods were defined the time through January 1, 2007 and the time after that date, respectively.

3. Calculated among children less than 5 years old eligible from birth.

4. * $p<0.05$ between pre and post vaccination rates.

Table 1 -7: Incremental PPPM costs of first RV Episode using two part model and Linear Models

	Commercial				Medi	
	PPPM Cost Differences[1,2] Adjusted, Two-Part Model		PPPM Cost Differences[1] Unadjusted (Linear Model)		PPPM Cost Differences[1,2] Adjusted, Two-Part Model	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
Overall	$3,615	($3,556 - $3,696)	$3,608	($3,540 - $3,676)	$2,106	($2,041 - $2,182)
Pre[3]	$3,792	($3,727 - $3,892)	$3,754	($3,672 - $3,819)	$2,080	($2,012 - $2,165)
Post[3]	$3,403	($3,306 - $3,524)	$3,399	($3,296 - $3,511)	$2,508	($2,213 - $2,748)

Notes:

CI = confidence interval; ER = emergency room; PPPM = per member per month; RV = rotavirus; SD = standa

*RV episodes with outlier costs (i.e., standard score is ±3.0 or beyond) among all RV episodes were excluded f

1. The p-value and CI of PPPM cost differences between RV episodes and matched control episodes were calcu
2. Estimated using a two-part model controlling for gender, race, and insurance plan type.
3. Pre- and post-RV vaccines were defined as before and on/after 01/01/2007, respectively.
4. Calculated among children less than 5 years old eligible from birth.

CHAPTER 2: Public health and cost impact of complete and incomplete rotavirus infection

Running Head: Complete and incomplete vaccination for rotavirus

Keywords: rotavirus, vaccination, diarrhea, cost, burden of illness, children

Target journal: to be determined
Word count (text limit – none at this time): 3,883
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ABSTRACT

Background: The clinical impact of RV5 is well established. On the other hand the impact of clinical and cost of rotavirus (RV) vaccinations (both Rotateq® and Rotarix®) as in current clinical practice during recent years' RV seasons are limited.

Methods: Beneficiaries who continuously received medical and pharmacy benefits since birth were identified separately in Truven Commercial Claims and Encounters (2000-2011) and Truven Medicaid Claims (2002-2010) and observed to end of eligibility or five years old. Infants, who received at least one RV vaccine dose within the ACIP-specified vaccination window of 6 weeks to 8 months old, will be divided into completely vaccinated and incomplete vaccination (i.e., after 8 months old). For children who did not receive any RV vaccine dose within the vaccination window, their observation time from 6 weeks old onward will be divided into historical unvaccinated (infants unvaccinated before 2007)after 8 months old and contemporary unvaccinated (infants unvaccinated after2007) after 8 months old. Comparisons between the two unvaccinated cohorts would be used to assess indirect effect of vaccination. Claims with International Classification of Disease 9th edition codes for diarrhea and RV were identified. Incidence of first RV episodes, RV-related and diarrhea-related healthcare resource utilization were calculated and compared across these groups. Poisson regressions were used to generate incidence rates 95% confidence intervals (CIs). Amortized mean total, inpatient, outpatient and emergency room costs for first RV episode, and RV-related and diarrhea-related costs were calculated. The bootstrapping method was used to evaluate difference in costs.

Results: There were 1,635,052 commercial and 664,387 Medicaid patients eligible from birth. Among the commercially insured infants incidence per 10,000 person-years among children

after 8 months among those who were completely vaccinated was 3.3 [95%CI: 2.8, 3.9], incomplete vaccinated 4.0 [95%CI: 3.3, 5.0], contemporary unvaccinated 20.9 [95%CI: 19.5, 22.4] and historical unvaccinated commercial cohort was 40.3 [95%CI 38.6,42.1]. Correspondingly among Medicaid was incidence per 10,000 person years among children after 8 months among those who were completely vaccinated was 7.5 [95%CI: 4.8, 11.8], incomplete vaccinated was 9.0 [95%CI: 6.5, 12.3], contemporary unvaccinated was 14.6 [95%CI: 12.8, 16.7], and historical unvaccinated was 52.0 [95%CI 50.2,53.8]. Amortized mean costs for first RV episode per patient was \$15.33 ($p<0.001$) and \$4.26 ($p<0.001$) lower in completed vaccinated cohorts versus contemporary unvaccinated cohort among commercially and Medicaid patients respectively, for children after 8 months. Amortized mean cost for first GE episode per patient was \$34.84 and \$21.69 ($p<0.05$) for commercial and Medicaid respectively.

Conclusions: Complete and incomplete RV vaccination confers benefits in RV episodes and mean cost of first episode. There is also evidence of strong indirect benefit comparing the two unvaccinated cohorts since the introduction of the vaccines.

INTRODUCTION

Rotavirus (RV) is the most common cause of severe diarrhea among children less than five years of age worldwide, accounting for greater than half a million deaths each year.[24] Although rarely fatal in the United States (US), RV remains a major cause of severe dehydration and hospitalization in children, thus incurring substantial healthcare resource utilization and costs. Before the initiation of a routine infant RV vaccination program in February 2006, nearly every child in the US was infected with RV by age five years (2.7 million episodes annually), resulting annually in approximately 410,000 outpatient visits (doctors office visits), 205,000-272,000 emergency room (ER) visits, 55,000-70,000 hospitalizations, and total annual direct and indirect costs of approximately $1 billion.[8-12;25]

Both the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics recommend routine immunization of infants with RV vaccine[12;13]. Two brands of oral RV vaccines are currently approved by the US Food and Drug Administration (FDA): Rotateq® (Merck & Co., Whitehouse Station, NJ, approved in 2006 in US) and Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium, approved in 2008 in US). The vaccine is administered in two doses if Rotarix is used; and in three doses if either Rotateq or a mix of brands (i.e., both Rotarix and Rotateq) is used. Irrespective of the brand of vaccine used, the ACIP recommends a vaccination window of six weeks old for the first dose and eight months and 0 days old for the last dose.[12] The 2011 National Immunization Survey (NIS) among children 19-35 months of age indicated that 67.3% received either at least two doses of Rotarix or at least three doses of Rotateq.[37]

Estimates of the clinical and economic impact of RV vaccination (including both Rotateq and Rotarix) among children aged less than five years, particularly during recent years' RV seasons, are limited. In addition, published studies to date using real-world practice data to evaluate complete and partial vaccine effectiveness have included only the Rotateq vaccine, and have not analyzed the Medicaid low-income population who are more susceptible to getting this information due to SES, crowding, hygiene,[1;18;31;38] Hence this study looks at the use of the vaccines in actual clinical practice.

The objectives of this study were to describe and compare clinical and economic outcomes among vaccinated and unvaccinated children during the ACIP recommended vaccination window, and to describe and compare the same outcomes among the vaccinated and unvaccinated children. Unlike past studies, this study has explored outcomes in both a commercially insured and Medicaid population. Outcomes were also compared to a cohort of unvaccinated children prior to the availability of vaccination to explore indirect benefits of the vaccine.

METHODS

Data Source

Data from the 2000-2011 Truven Commercial Claims and Encounters and the 2002-2010 Truven Medicaid databases were analyzed separately. Truven data are derived from insurance claims and contain 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, capitated or partially-capitated point-of-service, consumer-driven health plans, and high deductible health plans.

The Truven Commercial database contains claims from approximately 100 employers and a number of health plans. During the study period of 2000-2011, data from approximately nine million children under five years of age were captured. The Truven Medicaid database contains the pooled healthcare experience of approximately 7 million Medicaid enrollees from multiple states. During the study period of 2002-2010, data from approximately 4.5 million children under five years of age were captured. In both databases, variables include patient demographics, date of service, place of service (hospital, ER, urgent care facility, outpatient clinic), International Classification of Diseases 9th 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 (copay) to providers (i.e., physicians and hospitals). The data included in the Truven database are de-identified and are in compliance with the Health Insurance Portability and Accountability Act of 1996 to preserve participant anonymity and confidentiality.

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 weeks since birth. Due to the absence of birth dates in third party data cuts 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. Beneficiaries who enrolled in capitation-based health plans, and therefore may have incomplete claims, were excluded.

Study Design

A retrospective, longitudinal, open-cohort design was used for this study. Each eligible child was observed from his/her estimated birth date to end of continuous eligibility (i.e., due to disenrollment, data cut-off, or death) or five years of age, whichever occurred first. Individuals' person-time was partitioned into cohorts for the period from six weeks through 8 months old, and from 8 months old and onwards according to exposure to RV vaccines during the vaccination window (between 6 weeks and 8 months of age) to account for the age of the infant as risk of RV infection decreases with age. For the period from six weeks through 8 months old, children who received any RV vaccination during the vaccination window contributed person-time to the partial vaccination cohort; children who received no vaccination during this window contributed person-time to either the historical or contemporary unvaccinated cohort. The historical cohort was for individuals with birth year through 2006 and the contemporary cohort for individuals with birth year after 2006.

For the period from 8 months old, children who received two Rotarix, three Rotateq or three mixed type vaccinations during the vaccination window contributed person-time to the complete vaccination cohort; children who received less than complete vaccination but at least one during the vaccination window contributed person-time to the incomplete vaccination cohort; children who received no vaccination during the window contributed person-time to either the historical or contemporary unvaccinated cohort. During these periods, claims with the ICD-9 codes for diarrhea and/or RV were identified and used to describe the clinical and economic burden of RV by vaccination status. Comparisons between contemporary and historical unvaccinated were done to assess indirect effect of vaccination.

Study Outcomes

Clinical Outcomes

Clinical outcomes of interest included first episode of RV infection, RV-coded healthcare encounters (i.e., hospitalizations, outpatient visits, and ER visits), and diarrhea-coded healthcare encounters. As testing for RV is not performed routinely on all patients with diarrhea, claims coded as RV likely represent only a fraction of all RV-related encounters[10;24]; thus diarrhea-coded healthcare encounters were also of interest

RV-coded encounters were identified by claims with the specific ICD-9 code for RV (008.61 - Enteritis due to rotavirus). The first occurrence of an RV-coded encounter marked incidence of first 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 (Localized salmonella infections)) and 008.0-008.5 (Bacterial gastroenteritis), and 006.0-007.9 (excluding 006.3-006.6) (Parasitic gastroenteritis).

A claim identified as the primary discharge diagnosis or 1 of 15 other possible discharge diagnoses from inpatient admission data was classified as a hospitalization. An claim identified in 1 of the 2 diagnosis fields in the outpatient services data was classified as an outpatient visit. Encounters were classified as ER visits (i.e., not hospitalizations or outpatient visits) if “urgent care facility” or “emergency room” was specified in either the inpatient or outpatient services data. 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.

Economic Outcomes

Amortized mean costs was calculated for first diarrhea and RV episodes that occurred within each cohort by inpatient, outpatient and ER costs For each individual with a first RV episode, the costs incurred during the episode were summed. This calculation was done since the cost of a diarrhea or RV episode may be high but not last a long time; the amortized mean cost calculation can reflect this. RV-coded claims dated within 14 days of each other were used to identify the episode of first RV infection. The first RV episode was assumed to last from 14 days before the first RV-coded claim to 14 days after the last RV-coded claim of the episode (unless truncated by end of continuous eligibility). Individuals with no first RV episode had a cost of zero for cost of first RV episode. Similar methods were used to calculate the cost for diarrhea costs.

Statistical Analysis

Overall Cohort Description

For all eligible children, gender, year of eligibility start, health plan type, and race (for Truven Medicaid) were described, as well as vaccination cohort before 8 months and after 8 months. Frequencies and proportions were reported for categorical variables, while medians and ranges were reported for continuous variables.

Clinical Outcomes

Using data from the follow-up of each child, the incidence rates of first RV episodes, RV-coded healthcare encounters and diarrhea-coded healthcare encounters were calculated by dividing the total number of each event by the total person-years of observation for each vaccination cohort. The resulting incidence rates were reported as events per 10,000 persons per year. This person-time approach was used to account for different lengths of observation

among study subjects in a non-experimental setting. Poisson regressions were used to generate the incidence rates' 95% confidence intervals (CIs). Incidence rates were compared between vaccination cohorts by incidence rate ratios.

Economic Outcomes

Amortized mean total, inpatient, outpatient and ER costs were calculated for first RV and diarrheal episode by summing first episode costs for a cohort and dividing this by the number of individuals in the cohort. Standard deviations were also reported. The resulting costs were reported as dollars per 1,000 persons per year. Since cost data are often not normally distributed, the bootstrapping method was used to estimate the 95% CI of the difference in PPPY costs between vaccination cohorts. With the bootstrapping method, the patients within the vaccination cohort were sampled with replacement 500 times. Within each of the 500 resamples, a linear model was used to calculate the difference in PPPY cost for RV and diarrhea episode. The PPPY cost differences between the vaccination cohort were then used to determine the 95% CI using the percentile bootstrap method.

Analyses were stratified by age. For all cost analyses, costs were inflation-adjusted to 2012 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).

RESULTS

A total of 1,635,052 patients were included in the analysis of commercial data, and 664,387 patients were included in the analysis of Medicaid data (Table 2-1). Among the commercially insured children 73.8% were eligible from birth on or after 2006. In this

commercial population of children born on or after 2006, 66.2% of children had received at least one RV vaccine by 8 months of age. Forty four percent had completed the vaccination series per ACIP recommendation, and 22.43% had incomplete vaccination series per ACIP schedule.

In the Medicaid population, 44.9% were eligible from birth on or after 2006. Thirty two percent of children in this population born in 2006 or later had received at least one RV vaccine by 8 months of age. Among those born in 2006 or later, 12.9% had completed the vaccination series per ACIP, and 19.5% had incomplete vaccination series by 8 months of age. To validate the coding RV vaccination in the Medicaid population, the vaccination rate for DTaP was assessed. The DTaP vaccination rate in the Medicaid population in the study by 8 months of age was 40% and the corresponding rate as reported by CDC was 68% in 2009. Additionally we also evaluated the vaccination rate would be if we didn't exclude the capitated health plan patients. Vaccination rates for RV were approximately 35% completed vaccination and 60% had at least one RV vaccine.

Baseline Characteristics

Tables 2-2 and 2-4 describes the baseline characteristics of the various vaccination cohorts for the two populations. In both Medicaid and Commercial population the conditions most commonly diagnosed during birth to 8 months (vaccination windows) are similarly distributed among the 4 vaccination cohorts namely the completely vaccinated, Incomplete vaccinated, historical unvaccinated and the contemporary

unvaccinated. In the commercial population, the distribution of the type of health plan and the regions of the US are also similarly distributed.

Clinical Outcomes

Incidence of first RV episode is described in Table 2-4. The overall incidence in the commercial population and Medicaid populations was 19.0 (95%CI= 18.4, 19.6) and 43.5 (95%CI= 42.3, 44.8) cases per 10,000 persons per year, respectively. Among children after 8 months of age in the commercial population, the incidences per 10,000 persons per year in the completed vaccination cohort (3.3 [95%CI= 2.8, 3.9]) and incomplete vaccination cohort (4.0 [95%CI= 3.3, 5.0]) were statistically significantly less than the incidence in the contemporary unvaccinated cohort (20.9 [95%CI= 19.5, 22.4]). [Incidence Rate Ratio[IRR] IRR=0.17, 95%CI=(0.14,0.21) and IRR= 0.21, 95%CI=(0.16,0.27) respectively]. The incidence in the contemporary unvaccinated cohort (20.9 [95%CI= 19.5, 22.4]) was lower than that in the historical unvaccinated cohort (40.3 [95%CI 36.8,42.1] per 10,000 persons per year). [IRR=0.5, (95%CI=0.46,0.55)], indicating an indirect effect of protection. Among children before 8 months of age in the commercial population, the incidence per 10,000 persons per year in the partial vaccination cohort (5.2 [95%CI= 4.5, 6.1]) was lower than that in the contemporary unvaccinated cohort (13.8 [95%CI= 11.9, 15.9]); the incidence in the historical unvaccinated cohort was (33.0 [95%CI=30.7,35.5]).

As shown in Table 2-4, among children after 8 months of age in the Medicaid population, the incidences of first RV episode per 10,000 persons per year in the completed vaccination cohort was (7.5 [95%CI= 4.8, 11.8]) and incomplete vaccination cohort was (9.0

[95%CI= 6.5, 12.3]) and the incidence in the contemporary unvaccinated cohort (14.6 [95%CI 12.8, 16.7]). [IRR=0.68, 95%CI=(0.41, 1.12) and IRR= 0.62, 95%CI=(0.42, 0.91) respectively]. The incidence in the contemporary unvaccinated cohort was lower than that in the historical unvaccinated cohort (52.0 [95%CI= 50.2,53.8] per 10,000 persons per year). Among children less than 8 months of age in the Medicaid population, the incidence per 10,000 persons per year in the partial vaccination cohort (18.1 [95%CI= 14.2, 23.1]) was higher than that in the contemporary unvaccinated cohort (13.8 [95%CI= 11.1, 17.2]); both were lower than the incidence in the historical unvaccinated cohort (62.3 [95%CI= 59.0, 65.7] per 10,000 persons per year).

Table 2-5 describes the incidence of RV-related resource utilization for both the commercial and Medicaid populations. Among children after 8 months of age in the commercial population, the RV-related inpatient, outpatient and ER visit rates were significantly lower in the contemporary unvaccinated cohort compared with the historical unvaccinated cohort as demonstrated by the incidence rate ratios less than one (indicating a indirect benefit (herd effect). In this age group those completely vaccinated and incompletely vaccinated both had significantly lower RV-related inpatient, outpatient and ER visit rates compared with the contemporary unvaccinated cohort. The comparison of the completed vs the incomplete vaccinated had an IRR lower than 1 for all points of care, but only the inpatient visits was statistically significant. (IRR= 0.64 [95%CI= 0.42, 0.98]). Among children before 8 months old in the commercial population, RV-related resource utilization was significantly lower among the partial vaccinated versus contemporary unvaccinated. There were similar findings in the Medicaid population for children after 8 months. Except for the comparison of Inpatient visits

among completed vaccination vs contemporary unvaccinated, all other IRR between vaccination cohorts and unvaccinated cohorts were statistically significant. Among children before 8 months old in the Medicaid population, RV-related resource utilization was higher among the partial vaccinated versus contemporary unvaccinated cohort for inpatient and outpatient visits though not statistically significant ($p>0.05$). Clinical trials and observational studies of rotavirus vaccines have shown that the decreasing Vaccine efficacy (VE) of the vaccine is reduced in lowers SES: in high income settings demonstrated vaccine efficacy (VE) exceeding 90%.[31;39;40] In middle income settings of Latin America, South Africa and Vietnam, VE ranged from 72 to 83%,[41;42] while in low income settings in Asia and Africa, VE ranged from 39 to 49%.[42-44]

The incidence of diarrhea-related resource utilization for both the commercial and Medicaid populations is described in Table 2-6. Among children after 8 months in the commercial population, the diarrhea-related inpatient and outpatient visit rates were significantly ($p<0.05$) lower in the contemporary unvaccinated cohort compared with the historical unvaccinated cohort as demonstrated by the incidence rate ratios less than one. The diarrhea-related ER visit rate was significantly higher in the contemporary unvaccinated cohort compared with the historical unvaccinated cohort. In this age group those completely vaccinated and incompletely vaccinated both had lower diarrhea-related inpatient and ER visit rates compared with the contemporary unvaccinated cohort; the opposite was found for the outpatient visit rate. The completed vaccination cohort had a significantly lower incidence of Inpatient visits and ER visits compared to the incomplete vaccination cohort. [(inpatient IRR= 0.79 995%CI= 0.73, 0.87)0 and ER visits IRR=0.93 (95%CI= 0.90, 0.960]. Among children before 8

months in the commercial population, diarrhea-related inpatient and ER visits were significantly lower among the partial vaccinated versus contemporary unvaccinated; the opposite was found for the outpatient visit rate. Among children after 8 months in the Medicaid population, the diarrhea-related inpatient, outpatient visits and ER visit rates were significantly lower in the contemporary unvaccinated cohort compared with the historical unvaccinated cohort. Diarrhea-related resource utilization was higher in this age group for those completely vaccinated and incompletely vaccinated compared with the contemporary unvaccinated. Among children before 8 months in the Medicaid population, diarrhea-related resource utilization was higher among the partial vaccinated versus contemporary unvaccinated.

Economic Outcomes

The amortized mean cost per patient of first RV episode for the commercial and Medicaid populations are shown in Table 2-5. In the commercial population among children after 8 months, the amortized mean total cost, inpatient cost, outpatient cost and ER cost was lower for the contemporary unvaccinated versus historical unvaccinated cohort, for the completely vaccinated versus the contemporary unvaccinated cohort, and for the incompletely vaccinated versus the contemporary unvaccinated cohort; the differences were statistically significant ($p<0.05$). The mean cost difference among those who completed vaccination compared to those contemporary unvaccinated was \$15.32 ($p<0.0001$) and \$4.26 ($p<0.0001$) dollars lower per patient per year in commercial and Medicaid population respectively. Correspondingly the reduction in cost among those with incomplete vaccination compared to the contemporary unvaccinated was \$14.96 ($p<0.0001$) and \$3.77 ($p<0.001$) per patient per year in commercial

and Medicaid population respectively. The largest difference in the mean cost of first RV episode was among the inpatient costs among all comparisons For the children before 8 months in the commercial population, the amortized mean costs were lower in the partial vaccinated versus contemporary unvaccinated cohort, and the differences were statistically significant ($p<0.0001$). The effect among Medicaid was less clear in the before 8 months old comparisons.

The amortized mean cost per patient of first diarrhea episode for the commercial and Medicaid populations are shown in Table 2-6. In the commercial population among children after 8 months, the amortized mean total cost, inpatient cost, outpatient cost and ER cost was lower for the contemporary unvaccinated versus historical vaccinated cohort, completely vaccinated versus contemporary unvaccinated cohort, and incompletely vaccinated versus contemporary unvaccinated cohort; the differences were statistically significant ($p<0.05$). The mean total cost difference among those who completed vaccination compared to those contemporary unvaccinated was \$34.841 ($p<0.001$) and \$21.69 ($p=0.006$) dollars lower per patient in commercial and Medicaid population respectively. The largest difference in the mean cost of first RV episode was among the inpatient costs for comparisons against vaccinated and contemporary unvaccinated. The completed vaccination cohort had significantly lower costs per patient per year compared to the incomplete vaccination cohort for ER costs in commercial population and for total, inpatient and outpatient costs in Medicaid population.

DISCUSSION

In this study, since the introduction of the vaccine only 43.8% % of children in the commercial data (2010) and 12.9% of children in Medicaid data (2009) had completed vaccination according to ACIP guidelines (8 months of age). The CDC reported that 43% and 59% of children aged 19 to 35 mo were fully vaccinated against rotavirus in 2009 and 2010 respectively.[14] CDC also reported in 2009, 39% of infants had been vaccinated with Rotavirus vaccines by 7 months of age. To validate the coding for The DTaP vaccination rate in the Medicaid population in the study by 8 months of age was 40% and the corresponding rate as reported by CDC was 68% in 2009. When the data was not limited to the non capitated patients, the RV vaccination completion rates in Medicaid patients was 50%

Findings from the current study show that both complete and incomplete RV vaccination, including those achieved by mixed vaccination, result in significant reduction in RV infection for children after8 months old. The analysis of the commercial population shows that the incidence of RV infection among contemporary unvaccinated children was nearly five times higher than among complete and partially vaccinated children in the same period of time. The Medicaid analysis suggests a similar trend although the protection seen was not as strong but statistically significant. In both populations, the rate of RV was at least two fold higher among historical than contemporary unvaccinated children, indicating a strong indirect effect of the vaccine. Similar trends were seen with RV-related healthcare resource utilization. Benefits with partial vaccination were also observed for children before 8 months old. Although the study was not designed to compare rates among Medicaid and Commercial population, as seen

in multiple clinical and observational studies, this study also noticed lower reduction of disease among the vaccinated versus unvaccinated among the Medicaid patients compared to commercial population based on socio economic status (SES)[31;39;41-44].

The economic analysis of RV burden by vaccination cohort demonstrated lower cost burden as well for both complete and incomplete vaccination relative to unvaccinated children. In the commercial analysis for children after 8 months, the amortized mean total cost per patient per year for first RV episode was nearly fifteen dollars greater for unvaccinated children compared with completely and incompletely vaccinated children. The amortized mean total cost per patient per year for first RV episode was nearly $17 greater for unvaccinated children prior to the availability of vaccination compared with unvaccinated children after the availability of vaccine. Savings and similar trends for the same comparisons were seen in the in the Medicaid populations. Comparing the vaccinated (complete and incomplete cohorts) cohorts with the contemporary unvaccinated, the RV-related costs over the follow-up of the children showed significant cost savings among the vaccinated cohorts. There were also cost savings that were observed in first diarrheal episodes between the two populations.

The findings in this study on decline of RV infection following vaccination are in agreement with other published studies.[1;18;31;38] While prior studies demonstrated effectiveness of incomplete vaccination with Rotateq, none examined effectiveness of partial vaccination with Rotarix or mixed vaccination. In addition, not all children receive complete vaccination as demonstrated by these data which show that following vaccine availability 42.4% of children in the commercial data and 11.1% of children in Medicaid data had complete vaccination according to ACIP guidelines.

There are some limitations of the current study to consider. First, we examined data from only two and three post-vaccine RV seasons in Medicaid (2007-2009) and commercial (2007-2010) 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. Second, although we conducted stratified analysis by age and considered pre/post-RV vaccine availability in our analysis of unvaccinated children, we may not have accounted for all confounders. 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. Moreover, medical services obtained outside of a patient's plan are not captured in a claims database. Thus, there is the potential for exposure misclassification if an individual received vaccination outside a health plan, which is unlikely in the pediatric population in the US. In addition, resource utilization and costs in this study may be underestimated if a patient sought care outside his or her plan. Additionally the inability in both the data sources to adjust for socio-economic statuses must be considered as a limitation. However one could assume that the Medicaid population should be relatively homogenous compared to the commercially insured population.

This study which utilizes data from more than two million children in both commercial and Medicaid settings adds to our understanding of the benefits of RV vaccination. RV vaccination confers benefits both in terms of reduction in RV episodes, RV-related resource utilization and diarrheal related resource utilization. In addition, average patient costs due to RV and diarrheal episodes are substantially less among RV vaccinated cohorts in both populations.

ACKNOWLEDGEMENTS AND CONFLICT OF INTEREST

Table 2 1: Characteristics of eligible children in commercial and Medicaid population

Characteristic	Commercial N = 1,635,052	Medicaid N=664,387
Female, n (%)	667,795 (48.6%)	308,288 (48.6%)
Year of continuous eligibility start, n (%)		
2000	14,302 (1.0%)	0 (0.0%)
2001	19,638 (1.4%)	0 (0.0%)
2002	47,679 (3.3%)	83,240 (13.0%)
2003	74,625 (5.2%)	90,034 (14.0%)
2004	99,696 (7.0%)	88,904 (13.9%)
2005	117,695 (8.3%)	90,789 (14.2%)
2006	136,405 (9.6%)	99,240 (15.5%)
2007	163,245 (11.5%)	45,393 (7.1%)
2008	241,436 (16.9%)	46,317 (7.2%)
2009	259,684 (18.2%)	66,055 (10.3%)
2010	179,972 (12.6%)	30,932 (4.8%)
2011	71,010 (5.0%)	
Type of health plan, n (%)		
Comprehensive	26,676 (1.9%)	616,025 (96.1%)
Preferred provider organization	1,084,165 (76.1%)	831 (0.1%)
Other	314,546 (22.1%)	24,048 (3.8%)
Race, n (%)		
White	NR	365,752 (57.7%)
Black	NR	133,020 (21.0%)
Hispanic	NR	94,219 (14.9%)
Other	NR	40,843 (6.4%)
Vaccination cohort distribution, n (%)		
After 8 months old		
Completed Vaccination	321,615 (19.7%)	21,129 (3.2%)
Incomplete Vaccination	164,733 (10.1%)	31,951 (4.8%)
Historical Unvaccinated	335,090 (20.5%)	351,528 (52.9%)
Contemporary Unvaccinated	248,047 (15.2%)	110,969 (16.7%)
Before 8 months old		
Partial Vaccination	628,182 (38.4%)	73,602 (11.1%)
Historical Unvaccinated	483,221 (29.6%)	440,070 (66.2%)
Contemporary Unvaccinated	313,984 (19.2%)	127,232 (19.2%)
Vaccination Rates (%)		

Completed Vaccination	43.79%	12.88%
Incomplete Vaccination	22.43%	19.48%
Contemporary Unvaccinated	33.78%	67.64%

Abbreviations: NR, not reported.

Table 2-2: Baseline Characteristics, By Cohort: Commercial dataset

Characteristic	*Completed Vaccination* N = 321,615	*Incomplete Vaccination* N = 164,733	*U* N
Female, n (%)	156,907 (48.8%)	80,248 (48.7%)	162
Conditions most commonly diagnosed during the vaccination window[1]			
Acute upper respiratory infections of multiple or unspecified sites	125,450 (46.5%)	63,589 (46.4%)	125
Suppurative and unspecified otitis media	84,593 (31.3%)	46,524 (34.0%)	93,
Acute bronchitis and bronchiolitis	44,241 (16.4%)	25,430 (18.6%)	42,
General symptoms	52,351 (19.4%)	27,838 (20.3%)	41,
Symptoms involving respiratory system and other chest symptoms	48,870 (18.1%)	26,948 (19.7%)	38,
Diseases of esophagus	35,260 (13.1%)	14,506 (10.6%)	22
Viral and chlamydial infection in conditions classified elsewhere and of unspecified site	32,768 (12.1%)	17,775 (13.0%)	34,
Symptoms involving digestive system	25,892 (9.6%)	13,882 (10.1%)	22
Nonsuppurative otitis media and Eustachian tube disorders	22,750 (8.4%)	13,291 (9.7%)	26
Atopic dermatitis and related conditions	26,137 (9.7%)	12,708 (9.3%)	17
Type of health plan, n (%)			
Comprehensive	2,039 (0.6%)	1,541 (0.9%)	12
Preferred provider organization (PPO)	248,090 (77.1%)	121,886 (74.0%)	250
Other	71,486 (22.2%)	41,306 (25.1%)	71,
Region, n (%)			
Northeast	33,121 (10.3%)	18,476 (11.2%)	29
North Central	99,469 (30.9%)	42,817 (26.0%)	95,
South	146,077 (45.4%)	74,712 (45.4%)	162
West	39,630 (12.3%)	26,719 (16.2%)	43,
Unknown	3,318 (1.0%)	2,009 (1.2%)	3,

1. Conditions are listed in order of overall frequency of 3-digit ICD-9 codes in patients' medical claims during t
codes beginning with "V" are excluded from the table.

Table 2-3: Baseline Characteristics, By Cohort: Medicaid dataset

Characteristic	*Completed Vaccination* N = 21,129	*Incomplete Vaccination* N = 31,951
Female, n (%)	10,287 (48.7%)	15,412 (48.2%)
Conditions most commonly diagnosed during the vaccination window[1]		
Acute upper respiratory infections of multiple or unspecified sites	10,307 (54.9%)	14,148 (50.1%)
Suppurative and unspecified otitis media	5,880 (31.3%)	7,306 (25.9%)
Acute bronchitis and bronchiolitis	3,996 (21.3%)	5,989 (21.2%)
General symptoms	4,723 (25.2%)	6,802 (24.1%)
Symptoms involving respiratory system and other chest symptoms	4,881 (26.0%)	7,236 (25.6%)
Symptoms involving digestive system	3,030 (16.1%)	4,631 (16.4%)
Viral and chlamydial infection in conditions classified elsewhere and of unspecified site	2,895 (15.4%)	3,773 (13.4%)
Diseases of esophagus	3,048 (16.2%)	4,036 (14.3%)
Disorders relating to short gestation and low birthweight	676 (3.6%)	1,655 (5.9%)
Candidiasis	2,103 (11.2%)	3,011 (10.7%)
Type of health plan, n (%)		
Comprehensive	18,393 (87.1%)	28,427 (89.0%)
Preferred provider organization (PPO)	0 (0.0%)	0 (0.0%)
Other	2,736 (12.9%)	3,524 (11.0%)
Race, n (%)		
White	17,234 (81.6%)	22,420 (70.2%)
Black	1,612 (7.6%)	2,519 (7.9%)
Hispanic	909 (4.3%)	4,599 (14.4%)
Other	1,374 (6.5%)	2,413 (7.6%)

1. Conditions are listed in order of overall frequency of 3-digit ICD-9 codes in patients' medical claims during t
codes beginning with "V" are excluded from the table.

Table 2-4: Incidence of first RV episode in Commercial and Medicaid population

	Commercial			
	Incidence per 10,000 persons per year (95% CI)		Incidence rate ratio (95% CI)	Incidence per year (
	[A]	[B]	[A]/[B]	[C]
After 8 months old				
Contemporary vs. Historical Unvaccinated	Contemporary Unvaccinated	Historical Unvaccinated		Contemporary Unvaccinated
	20.2 (18.7-21.8)	40.3 (38.6-42.1)	0.50 (0.46-0.55)	12.6 (7.8-20.2)
Completed vs. Contemporary Unvaccinated	Completed Vaccinated	Contemporary Unvaccinated		Completed Vaccinated
	3.4 (2.8-4.1)	20.2 (18.7-21.8)	0.17 (0.14, 0.21)	12.6 (7.8-20.2)
Incomplete vs. Contemporary Unvaccinated	Incomplete Vaccinated	Contemporary Unvaccinated		Incomplete Vaccinated
	4.2 (3.4-5.3)	20.2 (18.7-21.8)	0.21 (0.16, 0.27)	11.4 (7.9-16.4)
Complete vaccinated vs Incomplete vaccinated				
Before 8 months old				
Partial Vaccinated vs. Contemporary Unvaccinated	Partial Vaccinated	Contemporary Unvaccinated		Partial Vaccinated
	5.3 (4.5-6.2)	13.2 (11.3-15.4)	0.40 (0.32, 0.50)	22.8 (17.9-29.0)

Abbreviations: CI, confidence interval; n/a, not applicable; vs, versus.

Table 2-5: Incidence of RV-coded hospitalizations, outpatient visits and ER visits in Commercial and Medicaid population

	Commercial			
	Incidence per 10,000 persons per year (95% CI)		Incidence rate ratio (95% CI)	Incidence per 1 (9
	[A]	[B]	[A]/[B]	[C]
After 8 months old				
Contemporary vs. Historical Unvaccinated	Contemporary Unvaccinated	Historical Unvaccinated		Contemporary Unvaccinated
Inpatient visits	12.2 (11.1-13.3)	24.4 (23.1-25.8)	0.50 (0.45-0.55)	7.2 (5.9-8.7)
Outpatient visits	13.6 (12.5-14.8)	21.6 (20.3-22.9)	0.63 (0.57-0.70)	9.4 (8.0-11.1)
ER visits	11.2 (10.2-12.3)	17.7 (16.5-18.9)	0.63 (0.57-0.71)	8.0 (6.6-9.6)
Completed vs. Contemporary Unvaccinated	Completed Vaccinated	Contemporary Unvaccinated		Completed Vaccinated
Inpatient visits	1.1 (0.9-1.5)	12.2 (11.1-13.3)	0.09 (0.07-0.13)	5.2 (3.0-8.9)
Outpatient visits	2.7 (2.3-3.3)	13.6 (12.5-14.8)	0.20 (0.16-0.25)	3.6 (1.9-6.9)
ER visits	1.1 (0.8-1.5)	11.2 (10.2-12.3)	0.10 (0.07-0.14)	1.6 (0.6-4.2)
Incomplete vs. Contemporary Unvaccinated	Incomplete Vaccinated	Contemporary Unvaccinated		Incomplete Vaccinated
Inpatient visits	1.8 (1.3-2.4)	12.2 (11.1-13.3)	0.15 (0.11-0.20)	4.0 (2.5-6.5)
Outpatient visits	2.9 (2.3-3.7)	13.6 (12.5-14.8)	0.21 (0.17-0.28)	6.1 (4.2-9.0)
ER visits	1.4 (1.0-2.0)	11.2 (10.2-12.3)	0.12 (0.09-0.18)	4.3 (2.7-6.7)
Complete Vaccinated vs Incomplete Vaccinated	Completed Vaccinated	Incomplete Vaccinated		Completed Vaccinated
Inpatient visits	1.1 (0.9-1.5)	1.8 (1.3-2.4)	0.64 (0.42-0.98)	5.2 (3.0-8.9)
Outpatient visits	2.7 (2.3-3.3)	2.9 (2.3-3.7)	0.94 (0.69-1.28)	3.6 (1.9-6.9)
ER visits	1.1 (0.8-1.5)	1.4 (1.0-2.0)	0.81 (0.51-1.28)	1.6 (0.6-4.2)
Before 8 months old				
Partial vs. Contemporary Unvaccinated	Partial Vaccinated	Contemporary Unvaccinated		Partial
Inpatient visits	1.9 (1.4-2.4)	7.5 (6.2-9.1)	0.25 (0.18-0.34)	11.8 (8.8-15.9)
Outpatient visits	4.9 (4.2-5.8)	9.4 (7.9-11.2)	0.52 (0.41-0.66)	12.1 (9.0-16.2)

ER visits	1.9 (1.5-2.4)	7.6 (6.3-9.3)	0.25 (0.18-0.34)	7.4 (5.1-10.8)

Abbreviations: CI, confidence interval; vs, versus.

Table 2-6: Incidence of diarrhea-coded hospitalizations, outpatient visits and ER visits in commercial and Medicaid population

	Commercial			Medicaid	
	Incidence per 10,000 persons per year (95% CI)		Incidence rate ratio (95% CI)	Incidence per 10,000 persons per year (9	
	[A]	[B]	[A]/[B]	[C]	[D]
After 8 months old					
Contemporary vs. Historical Unvaccinated	Contemporary Unvaccinated	Historical Unvaccinated		Contemporary Unvaccinated	Histori Unvaccinat
Inpatient visits	53. 5 (51.2-55.8)	72.7 (70.4-75.1)	0.74 (0.70-0.78)	60.4 (56.5-64.6)	86.9 (84.6-8
Outpatient visits	1,845.4 (1,832.0-1,858.9)	1,961.5 (1,949.4-1,973.8)	0.94 (0.93-0.95)	1,875.0 (1,852.8-1,897.5)	1,959 (1,948.2-1,9
ER visits	271.7 (266.6-276.9)	253.8 (249.5-258.2)	1.07 (1.04-1.10)	547.8 (535.9-560.1)	721. (714.6-7
Completed vs. Contemporary Unvaccinated	Completed Vaccinated	Contemporary Unvaccinated		Complete Vaccinated	Contemp Unvaccinat
Inpatient visits	29.4 (27.7-31.1)	53.5 (51.2-55.8)	0.55 (0.51-0.59)	75.0 (65.1-86.5)	60.4 (56.5-6
Outpatient visits	2,068.4 (2,054.3-2,082.5)	1,845.4 (1,832.0-1,858.9)	1.12 (1.11-1.13)	2,831.6 (2,766.6-2,898.1)	1,875 (1,852.8-1,8
ER visits	209.0 (204.5-213.5)	271.7 (266.6-276.9)	0.77 (0.75-0.79)	716.3 (684.0-750.2)	547. (535.9-5
Incomplete vs. Contemporary Unvaccinated	Incomplete Vaccinated	Contemporary Unvaccinated		Incomplete Vaccinated	Contemp Unvaccinat
Inpatient visits	37.0 (34.5-39.6)	53.5 (51.2-55.8)	0.69 (0.64-0.75)	73.0 (65.3-81.6)	60.4 (56.5-6
Outpatient visits	1,918.0 (1,899.9-1,936.2)	1,845.4 (1,832.0-1,858.9)	1.04 (1.03-1.05)	2,724.3 (2,675.0-2,774.4)	1,875 (1,852.8-1,8
ER visits	225.1 (219.0-231.4)	271.7 (266.6-276.9)	0.83 (0.80-0.86)	708.3 (683.4-734.2)	547. (535.9-5
Complete Vaccinated vs Incomplete Vaccinated	Completed Vaccinated	Incomplete Vaccinated		Completed Vaccinated	Incomp Vaccinate
Inpatient visits	29.4 (27.7-31.1)	37.0 (34.5-39.6)	0.79 (0.73-0.87)	75.0 (65.1-86.5)	73.0 (65.3-8
Outpatient visits	2,068.4 (2,054.3-2,082.5)	1,918.0 (1,899.9-1,936.2)	1.08 (1.07-1.09)	2,831.6 (2,766.6-2,898.1)	2,724 (2,675.0-2,7
ER visits	209.0 (204.5-213.5)	225.1 (219.0-231.4)	0.93 (0.90-0.96)	716.3 (684.0-750.2)	708. (683.4-7
Before 8 months old					
Partial vs. Contemporary Unvaccinated	Partial Vaccinated	Contemporary Unvaccinated		Partial Vaccinated	Contemp Unvaccinat
Inpatient visits	49.8 (47.4-52.3)	70.1 (65.7-74.7)	0.71 (0.66-0.77)	146.7 (134.8-159.7)	97.9 (90.2-10
Outpatient visits	2,010.8 (1,995.2-2,026.4)	1,911.5 (1,888.2-1,935.1)	1.05 (1.04-1.07)	2,656.9 (2,604.5-2,710.4)	1,764 (1,730.9-1,7

ER visits	231.4 (226.2-236.8)	288.6 (279.7-297.9)	0.80 (0.77-0.83)	827.0 (798.0-857.1)	565. (546.3-5

Abbreviations: CI, confidence interval; vs, versus.

Table 2-7: Amortized mean cost per patient per year of the First RV episode in commercial and Medicaid population

	Commercial			
	Mean($2012) ± SD		Difference ($2012)	Mean($20
	[A]	[B]	[A]-[B]	[C]
After 8 months old				
Contemporary vs. Historical Unvaccinated	Contemporary Unvaccinated	Historical Unvaccinated		Contemporary Unvaccinated
Total costs	17,091.9 ± 626,240.5	34,659.4 ± 626,497.1	-17,567**	6,025.2 ± 279,180.5
Inpatient costs	11,698.4 ± 535,406.7	23,415.5 ± 500,842.6	-11,717**	4,444.6 ± 238,398.1
Outpatient costs	3,012.4 ± 123,464.4	6,460.8 ± 200,929.5	-3,448**	1,062.5 ± 68,448.9
ER costs	2,381.1 ± 74,735.7	4,783.1 ± 116,196.1	-2,402**	518.1 ± 25,624.0
Completed vs. Contemporary Unvaccinated	Completed Vaccinated	Contemporary Unvaccinated		Completed Vaccinated
Total costs	1,763.9 ± 227,607.0	17,091.9 ± 626,240.5	-15,328**	1,762.1 ± 78,367.9
Inpatient costs	1,228.1 ± 211,359.9	11,698.4 ± 535,406.7	-10,470**	1,365.4 ± 67,321.9
Outpatient costs	330.7 ± 28,297.3	3,012.4 ± 123,464.4	-2,682**	274.6 ± 13,997.6
ER costs	205.0 ± 20,179.1	2,381.1 ± 74,735.7	-2,176**	122.2 ± 7,637.2
Incomplete vs. Contemporary Unvaccinated	Incomplete Vaccinated	Contemporary Unvaccinated		Incomplete Vaccinated
Total costs	2,128.3 ± 169,594.8	17,091.9 ± 626,240.5	-14,964**	2,252.3 ± 125,164.6
Inpatient costs	1,371.5 ± 129,182.2	11,698.4 ± 535,406.7	-10,327**	1,668.0 ± 117,681.5
Outpatient costs	419.3 ± 34,842.2	3,012.4 ± 123,464.4	-2,593**	406.2 ± 17,787.1
ER costs	337.5 ± 39,712.7	2,381.1 ± 74,735.7	-2,044**	178.1 ± 8,294.5
Complete Vaccinated vs Incomplete Vaccinated				
Total costs	1,763.9 ± 227,607.0	2,128.3 ± 169,594.8	-364	1,762.1 ± 78,367.9
Inpatient costs	1,228.1 ± 211,359.9	1,371.5 ± 129,182.2	-143	1,365.4 ± 67,321.9
Outpatient costs	330.7 ± 28,297.3	419.3 ± 34,842.2	-89	274.6 ± 13,997.6
ER costs	205.0 ± 20,179.1	337.5 ± 39,712.7	-133	122.2 ± 7,637.2
Before 8 months old				
Partial vs. Contemporary Unvaccinated	Partial Vaccinated	Contemporary Unvaccinated		Partial Vaccinated
Total costs	2,352.0 ± 215,433.0	13,217.2 ± 651,615.5	-10,865**	5,099.2 ± 303,641.5
Inpatient costs	1,597.4 ± 192,276.0	9,349.6 ± 581,649.2	-7,752**	4,163.7 ± 295,906.5
Outpatient costs	459.2 ± 33,872.6	2,110.2 ± 101,686.2	-1,651**	629.4 ± 27,219.8
ER costs	295.5 ± 27,885.5	1,757.4 ± 77,334.2	-1,462**	306.0 ± 12,292.9

Abbreviations: SD, standard deviation; vs, versus.
* = p-value <0.05; ** = p-value <0.001;

Table 2-8: Amortized mean cost per patient per year of first diarrhea episode

	Commercial			
	Cost per 1,000 persons per year Mean($2012) ± SD		Difference ($2012)	Cost per 1,000 Mean($
	[A]	[B]	[A]-[B]	[C]
After 8 months old				
Contemporary vs. Historical Unvaccinated	Contemporary Unvaccinated	Historical Unvaccinated		Contemporary Unvaccinated
Total costs	142,193.7 ± 2,702,570.7	199,950.2 ± 3,525,724.7	-57,756**	87,688.7 ± 2,183,654.7
Inpatient costs	58,382.4 ± 2,528,631.1	82,341.8 ± 3,411,921.7	-23,959**	43,184.8 ± 2,093,868.2
Outpatient costs	57,759.1 ± 591,698.5	82,610.4 ± 489,460.6	-24,851**	31,539.7 ± 249,982.1
ER costs	26,052.2 ± 263,404.8	34,997.9 ± 257,542.3	-8,946**	12,964.2 ± 169,192.4
Completed vs. Contemporary Unvaccinated	Complete Vaccinated	Contemporary Unvaccinated		Complete Vaccinated
Total costs	107,352.4 ± 3,537,254.8	142,193.7 ± 2,702,570.7	-34,841**	65,998.0 ± 659,062.8
Inpatient costs	38,716.1 ± 3,464,543.9	58,382.4 ± 2,528,631.1	-19,666*	21,630.6 ± 582,291.6
Outpatient costs	51,536.2 ± 405,613.6	57,759.1 ± 591,698.5	-6,223**	30,359.1 ± 159,546.4
ER costs	17,100.1 ± 164,001.2	26,052.2 ± 263,404.8	-8,952**	14,008.3 ± 87,755.1
Incomplete vs. Contemporary Unvaccinated	Incomplete Vaccinated	Contemporary Unvaccinated		Incomplete Vaccinated
Total costs	117,875.1 ± 2,488,243.1	142,193.7 ± 2,702,570.7	-24,319**	92,544.9 ± 1,923,251.1
Inpatient costs	45,770.4 ± 2,372,629.1	58,382.4 ± 2,528,631.1	-12,612	39,706.5 ± 1,849,956.1
Outpatient costs	51,448.7 ± 359,320.8	57,759.1 ± 591,698.5	-6,310**	38,774.1 ± 238,878.6
ER costs	20,656.0 ± 275,207.6	26,052.2 ± 263,404.8	-5,396**	14,064.3 ± 91,066.9
Complete vs Incompletely vaccinated	Complete Vaccinated	Incomplete Vaccinated		Complete Vaccinated
Total costs	107,352.4 ± 3,537,254.8	117,875.1 ± 2,488,243.1	-10,523	65,998.0 ± 659,062.8
Inpatient costs	38,716.1 ± 3,464,543.9	45,770.4 ± 2,372,629.1	-7,054	21,630.6 ± 582,291.6
Outpatient costs	51,536.2 ± 405,613.6	51,448.7 ± 359,320.8	88	30,359.1 ± 159,546.4
ER costs	17,100.1 ± 164,001.2	20,656.0 ± 275,207.6	-3,556**	14,008.3 ± 87,755.1
Before 8 months old				
Partial vs. Contemporary Unvaccinated	Partial Vaccinated	Contemporary Unvaccinated		Partial Vaccinated
Total costs	161,285.1 ± 3,916,736.5	188,984.9 ± 4,017,408.4	-27,700**	144,542.7 ± 2,653,706.5
Inpatient costs	68,183.5 ± 3,819,694.6	101,954.9 ± 3,876,344.2	-33,771**	75,029.3 ± 2,583,891.4
Outpatient costs	69,194.1 ± 425,990.3	60,654.0 ± 444,675.3	8,540**	49,084.9 ± 245,849.8
ER costs	23,907.6 ± 283,908.7	26,375.9 ± 293,083.8	-2,468**	20,428.5 ± 112,011.1

bbreviations: SD, standard deviation; vs, versus.

* = p-value <0.05; ** = p-value <0.001;

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Overall Conclusions and Summary

Rotavirus diseases in the US are rarely fatal, but have been a major cause of severe hydration and hospitalization in children. There are two vaccines that are approved by FDA for prevention of rotavirus disease: Rotarix (2009) and Rotateq (2006).

The results from the burden of disease suggest that the overall incidence rates of first RV episode among children less than 5 years of among commercial and Medicaid are 17.34 (95%CI: 17.04-17.64) and 34.53 (95% CI: 33.75-35.32) respectively. Both populations showed a reduction of 58% and 44% in incidence of the first RV episode since the introduction of the vaccines in 2006. In both populations, incidence of RV-coded encounters among children less than 5 years of age declined significantly following introduction of RV vaccines, with the exception of outpatient visits in Medicaid where the slight decline was not significant. As shown in Table 1-3, incidence rates of RV for children <5 years old in the commercial population declined by 67% for hospitalizations, 28% for outpatient visits, and 57% for ER visits. The corresponding percentage declines in the Medicaid population were 47% for hospitalizations, 5% for outpatient visits, and 67% for ER visits. The total per patient per month cost for first RV episode in the post vaccination period was $ 3399 (95%CI: 3289-3511) and $2291 (95%CI: 2085-2504) in commercial and Medicaid population respectively.

In the second chapter the study looked at the impact of vaccination of RV and diarrhea related clinical and cost outcomes. The vaccination rates after 8 months of age among the commercial population for any RV vaccination, completed RV vaccination and unvaccinated between 2006-2010 were 66.2%, 43.8% and 33.8%. The corresponding rates for Medicaid for any RV vaccination, completed RV vaccination and unvaccinated between 2006-2009 were 32.4%, 12.88% and 67.6%. The data also showed that both complete and incomplete RV vaccination result in reduction in RV infection for children after 8 months of age for both population. In addition the data showed strong indirect herd effect in both populations when comparing incidence of first RV episode between the contemporary

unvaccinated and historical unvaccinated population. (IRR in commercial and Medicaid are: 0.50 (95%CI: 0.46-0.55) and 0.36 (95%CI: 0.31-0.41)

There are several limitations that one must bear in mind when interpreting the results from this research. First we examined data from only 2 and 3 post vaccine RV season in Medicaid (2007-2010) and commercial (2007-2011) and cannot be certain that all changes were due to solely to vaccine use. Secondly ICD 9 codes were used to identify diagnosis; and these codes may not reflect confirmed clinical diagnosis and lack information to assess severity of illness. Additionally the data collected are for billing and insurance proposes and therefore may have its own limitations in the use in research.

However despite these limitations, this research adds valuable information to the literature. The burden of disease or the impact of rotavirus vaccination among Medicaid population has not been published in the past, and this study adds further insight into this population. Additionally the impact on the potential cost savings between the vaccinated cohorts has not been addressed previously.

Hence in conclusion, since the introduction of the vaccine, the burden of disease has decreased in both commercial and Medicaid population and vaccination confers protection against RV disease.