PATTERNS OF ROTAVIRUS VACCINE UPTAKE, USE, AND EFFECTIVENESS IN PRIVATELY-INSURED US CHILDREN, 2006-2010

Catherine A. Panozzo

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Approved by:

M. Alan Brookhart

Sylvia Becker-Dreps

Michele Jonsson Funk

Til Stürmer

David J.Weber

ABSTRACT

CATHERINE A. PANOZZO: Patterns of rotavirus vaccine uptake, use, and effectiveness in privately-insured US children, 2006-2010
(Under the direction of M. Alan Brookhart)

Objectives. Our study examines predictors and timeliness of rotavirus vaccine administration among privately-insured US infants and children from 2006 to 2010. We also calculate direct, indirect, total, and overall rotavirus vaccine effectiveness estimates as well as the number of rotavirus and acute gastroenteritis hospitalizations prevented among infants and children aged 8 to 20 months.

Methods. Bivariate analyses and multivariable log-risk models were used to determine predictors of rotavirus vaccine series initiation and completion among infants in the MarketScan Research Databases. Vaccine effectiveness estimates were derived using Cox proportional hazards regression, stratifying by calendar year and adjusting for month of birth. Incidence rate differences were calculated to determine the absolute number of rotavirus and acute gastroenteritis hospitalizations prevented in the cohort.

Results. Most infants received the rotavirus vaccines at the recommended ages, but more infants completed the series for monovalent rotavirus vaccine than pentavalent rotavirus vaccine or a mix of the two vaccines (87% versus 79% versus 73%). In multivariable analyses, the strongest predictors of rotavirus vaccine series initiation and completion were

receipt of the diphtheria, tetanus and acellular pertussis vaccine (Initiation: RR=7.50, 95% CI=7.30-7.71; Completion: RR=1.26, 95% CI=1.23-1.29), visiting a pediatrician versus family physician (Initiation: RR=1.51, 95% CI=1.49-1.52; Completion: RR=1.13, 95% CI=1.11-1.14), and living in a large metropolitan versus smaller metropolitan, urban, or rural area. Direct vaccine effectiveness of one or more doses of any rotavirus vaccine in preventing rotavirus gastroenteritis hospitalizations in children 8 to 20 months ranged from 87 to 92% for each calendar year, 2007-2010. Accounting for indirect protection increased the total vaccine effectiveness by an additional 3 to 8%. Failing to account for indirect protection underestimated the absolute number of rotavirus gastroenteritis hospitalizations prevented in rotavirus-vaccinated children by 1.5 to 5.3-fold.

Conclusions. Accounting for only the direct effectiveness of the rotavirus vaccine severely underestimated the total number of rotavirus gastroenteritis hospitalizations prevented by the US rotavirus vaccine program. Interventions to further increase rotavirus vaccine coverage should consider targeting family physicians and encouraging completion of the vaccine series.

PREFACE

If successfully awarded this Doctor of Philosophy in Epidemiology, I will be the first "doctor" of any kind in the Panozzo and Marks family.

This achievement would not be close to being realized without support from my parents, Don and Susan Panozzo, and my fiancée, Jeremy Marks.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACIP: Advisory Committee on Immunization Practices

AGE: acute gastroenteritis

CDC: Centers for Disease Control and Prevention

CDHP: Consumer Directed Health Plan

CI: confidence interval

CPT: Current Procedural Terminology

DTaP: diphtheria, tetanus, and acellular pertussis vaccine

DTP: diphtheria, tetanus, and pertussis vaccine

EPO: Exclusive Provider Organization

FDA: Food and Drug Administration

FIPS: Federal Information Processing Codes

HHS: Health and Human Services

HMO: Health Maintenance Organization

ICD-9-CM: International Classification of Diseases, 9^{th} Revision, Clinical Modification

IQR: Interquartile range

IRD: Incident rate difference

Metro: Metropolitan

NC DETECT: North Carolina Disease Event Tracking and Epidemiologic Collection Tool

NCIR: North Carolina Immunization Registry

NIS: National Immunization Survey

OPV: oral polio vaccine

PCV: porcine circovirus

Pop: population

POS: Point of Service, or Point of Service with capitation

PPO: Preferred Provider Organization

RGE: rotavirus gastroenteritis

RRV-TV: rhesus rotavirus vaccine, tetravalent

RV1: monovalent rotavirus vaccine

RV5: pentavalent rotavirus vaccine

Std: standard deviation

US: United States

USDA: United States Department of Agriculture

V: vaccinated

VE: vaccine effectiveness

VFC: Vaccines for Children

CHAPTER I

REVIEW OF THE LITERATURE

A. Conceptual framework

Measuring vaccine effectiveness post-market. Post licensure vaccine effectiveness (VE) studies present both challenges and new opportunities. On one hand, since post licensure studies are not generally randomized, identical exposure rates to infections in vaccinated and unvaccinated individuals cannot be guaranteed or always measured. Additional concerns may include potential biases in case ascertainment, case finding, and the validity of vaccination and disease records.(1, 2) On the other hand, the duration of vaccine protection, changing epidemiologic patterns of disease, and effectiveness among diverse populations, including those vaccinated on alternative schedules, can only be investigated post licensure.(3)

Definitions of vaccine effectiveness. Most Phase III vaccine efficacy trials focus on determining the direct effectiveness of vaccination, generally measured as one minus the relative risk in the vaccinated group compared to the unvaccinated group. Some clinical trials and many post-licensure studies also measure herd protection or indirect vaccine effectiveness (VE), defined as population-level effects of widespread vaccination on people not receiving the vaccine.(1) Two additional measures of VE, total and overall VE, account for both the direct and indirect effectiveness of a vaccine. Total VE combines the direct and

indirect VE on individuals receiving the vaccine, while the overall VE weights the average of the total VE on individuals receiving the vaccine with the indirect VE on individuals not receiving the vaccine.(1) Total VE can thus be interpreted as the complete benefit of vaccination in vaccine recipients and overall VE can be interpreted as the public health benefit of vaccination. Despite challenges in estimating the four types of VE, they are essential to understand the real-world impact of a vaccine. (1-3)

B. Historical background

Epidemiology of acute gastroenteritis (AGE) and rotavirus gastroenteritis (RGE). Although there are many viral, bacterial, and parasitic causes of acute gastroenteritis (AGE) in the US, viruses are the most common causes of infectious diarrhea across all age groups, and among viruses, rotavirus and norovirus are most frequently observed.(4, 5) Prior to the availability of rotavirus vaccines in 2006, AGE accounted for approximately nine percent of all hospitalizations among children less than five years of age in the US, and of the 220,000 children in this age group hospitalized with AGE annually, one-quarter to one-third of these hospitalizations were due to rotavirus infection.(6-9)

In an analysis of privately insured US children during the pre-rotavirus vaccine era, 2001-2006, the average annual rate of healthcare utilization across all healthcare settings for AGE was 1561 per 10,000 children less than five years of age. The annual hospitalization rate for AGE was 50 per 10,000, the emergency department visit rate was 180 per 10,000, and outpatient visit rate was 1332 per 10,000 children less than five years of age. With regards to rotavirus gastroenteritis (RGE), during the first five years of life, 1 in 74 children were admitted, 1 in 27 required emergency department care, and 1 in 7 were treated

in outpatient settings each year.(10) Health care utilization estimates from another study utilizing claims data found that the AGE and RGE hospitalization rates among children less than five years of age with Medicaid insurance were nearly double the estimates reported for children with private insurance during the pre-rotavirus vaccine period (107 versus 41 per 10,000); however, outpatient and emergency department estimates among children with both insurance types were similar.(11)

In the pre-rotavirus vaccine era, virtually all children became infected with rotavirus by age three years, with illness most commonly occurring between four and twenty-four months of age. Infections during the first three months of life and reinfections among older children were more likely to be asymptomatic than primary infections in older infants and younger children.(4) Rotavirus transmission is presumed to occur via the fecal-oral route, and shedding has been observed up to 21 days after symptom onset.(4) In the US, prior to the availability of rotavirus vaccines, rotavirus was most prevalent during the winter and spring months, generally peaking in March.(12-14) Since the availability of rotavirus vaccines, the typical winter-spring seasonality of rotavirus has shown signs of disruption in the US.(14, 15)

Rotavirus illness usually begins with acute onset of fever and vomiting followed by water diarrhea with 10 to 20 bowel movements per day.(16) Such symptoms generally persist for three to eight days.(4) No specific antiviral therapy is available so treatment generally consists of oral or parenteral fluids to prevent and correct dehydration.(17) Dehydration and electrolyte disturbances are the major complications of rotavirus infection, and are most common in young infants.(4) Worldwide, complications from rotavirus infection approximately 453,000 deaths annually, or six percent of all deaths in children less than five

years of age.(18) In the US, rotavirus infections are not a major cause of mortality since therapy for dehydration is readily available.(19)

History of rotavirus vaccines. The first rotavirus vaccine that was licensed and recommend for routine use in US infants was rhesus rotavirus vaccine, tetravalent (RRV-TV), or Rotashield (Wyeth). It was composed of four live viruses, including three reassortants expressing either G1, G2, or G4 proteins, and the native G3P[3] strain.(20) RRV-TV was an oral vaccine, given as a three dose series at ages two, four, and six months.(20) After approximately one year of availability (1998-1999), the recommendation to routinely vaccinate infants with RRV-TV was withdrawn due to its association with intussusception, a type of bowel obstruction that occurs when the bowel folds in on itself (relative risk, 1.6 – 1.8).(21-23)

Due to the experience of RRV-TV, a major safety concern when developing new rotavirus vaccines was their potential association with intussusception.(24) Although two large clinical trials (>60,000 infants) powered to assess intussusception risk at a magnitude similar to that of RRV-TV did not find an increased risk of intussusception after vaccination with either of the two currently available rotavirus vaccines, two post-marketing studies found a potential increased risk of intussusception following rotavirus vaccination with monovalent rotavirus vaccine (RV1), and one of these studies also found an increased risk of intussusception after pentavalent rotavirus vaccine (RV5) vaccination.(25-34) However, neither of these studies was conducted in the US, and the increased risk of intussusception was not consistent for a given dose across the different populations of Mexican, Brazilian, and Australian infants.(25, 26) To-date, RV5 and RV1 continue to be recommended for US infants.

RV5 was licensed and recommend in February 2006, and RV1 was licensed in April 2008 and recommended in June 2008 for routine use among US infants by the Advisory Committee on Immunization Practices (ACIP).(35, 36) RV5 contains five reassortant rotaviruses developed from human and bovine parent strains that express proteins from serotypes G1, G2, G3, G4, and P1A[8], and RV1 consists of a single attenuated human rotavirus strain of the G1P1A[8] serotype. Both are live, oral vaccines, but RV5 requires three doses administered at ages two, four, and six months and elicits mainly a homotypic immune response, while RV1 requires just two doses administered at ages two and four months and is thought to elicit both a homotypic and heterotypic immune response.(36)

On March 22, 2010 the Food and Drug Administration (FDA) recommend that physicians suspend the use of RV1 after academic researchers discovered that the vaccine contained DNA from porcine circovirus 1 (PCV1).(37) Although the FDA emphasized that there were no known safety risks associated with PCV1 contamination, they advised physicians to switch to RV5 which was later found to be contaminated with PCV1 and porcine circovirus 2 (PCV2). By May 2010, the FDA recommended that physicians resume the use of RV1 and continue use of RV5 since PCV1 and PCV2 are not known to cause illness in either pigs or humans. The labels of both vaccines were updated to disclose the presence of PCV viruses.(37)

History of rotavirus vaccine recommendations. The 2006 ACIP recommendations for RV5 allowed the first dose to be administered between 6—12 weeks of age with subsequent doses administered at 4—10 week intervals so that all three doses could be administered by age 32 weeks.(35) Since RV1 was administered at slightly different ages in clinical trials and the ACIP wanted to unify recommendations for the two rotavirus vaccines, the ACIP

recommendations changed when RV1 was licensed. The 2009 ACIP recommendations increased the new maximum age at which the first dose could be administered to 14 weeks, 6 days, and the maximum age at which the last dose could be administered to 8 months, 0 days (~35 weeks). They also eliminated the maximum interval at which a dose could be given.(36) The 2009 ACIP guidelines apply to both RV5 and RV1 and continue to be used in practice.

C. Critical review of the literature

Predictors of vaccine uptake. Among eight recommended pediatric vaccines, only the hepatitis A vaccine has lower coverage than the rotavirus vaccine in the US (50% versus 59%).(38) Not much is known about why newly adopted vaccines like the rotavirus vaccine can take years to reach high coverage levels, but individual, provider, and ecologic characteristics likely play a role. At the individual level, parents or guardians may consciously choose not to vaccinate their children with any, many, or certain vaccines for personal reasons such as the fear of side effects, or the belief that vaccines are not necessary to protect child health.(39) Some studies have also shown that children of young mothers may also be less likely to be up-to-date on their vaccines than children with older mothers, but this finding has been inconsistent across different geographic settings and populations.(40-43) Few studies have specifically examined individual-level predictors of rotavirus vaccine uptake. However, one analysis of 2009 National Immunization Survey (NIS) data found that rotavirus and pneumococcus vaccine coverage among black, non-Hispanic children was lower than coverage among white, non-Hispanic children, even after adjusting for poverty status.(44) Other individual-level predictors inconsistently associated

with childhood immunization status include gender, maternal education, birth order, interbirth interval, and frequency of emergency room visits.(42, 43, 45-50)

With regards to provider characteristics, having consistent continuity of care can impact the quality of care received, and physician office size, clinic hours, reimbursement levels, patient volume, patient education efforts, and geographic location of the office may also impact whether a recommended vaccine is administered.(51-62) The type of physician visited may also influence whether an infant receives a rotavirus vaccine. A national survey of physicians in 2007 found that while 85% of pediatricians routinely offered the rotavirus vaccine, only 45% of family medicine physicians routinely offered it to eligible patients.(61) Other provider, health plan, or health plan utilization characteristics that have been associated with the timeliness or completion of recommended childhood vaccines include status of provider (private versus public), insurance status of patient (uninsured versus insured), number of patient visits to provider, consistency of medical home, and out-of-pocket expenses.(41, 43, 48, 49, 62)

Geographic characteristics of residence, including the population density, region of the country, and population size of the metropolitan statistical area have been important predictors of childhood immunization status in some studies, and unimportant in others.(45, 46, 49, 50, 55, 59) Additional ecologic factors, such as number of physicians per person and income level in the area residence, have also been explored.(43, 46) One study using NIS data to measure vaccine coverage among preschool children in four selected medically underserved areas found that an area's need for childhood vaccination interventions was not well predicted by a low number of providers per capita, but this finding has not been replicated elsewhere.(43) Another study found that children attending schools in census

tracts with low per capita incomes that did not receive first and second doses of DTP and oral polio vaccine (OPV) simultaneously were much less likely to be age-appropriately vaccinated by age two years compared with children attending schools in census tracts with higher per capita incomes that received the first and second doses of DTP and OPV simultaneously.(46)

Timeliness of rotavirus vaccine administration. Administering the rotavirus vaccines at the recommended times (i.e., according to the current ACIP guidelines) is considered important because the effectiveness and safety of the vaccines if given before or after the recommended time intervals are currently unknown. However, some studies have argued that the allowable administration window should be broadened because the potential number of excess deaths from adverse events (i.e., intussusception) would be outnumbered by the number of lives saved from diarrheal disease if more infants could receive a rotavirus vaccine.(25, 63)

A recent study using the health insurance claims database, Optuminsight, noted a slightly higher level of adherence to the 2009 ACIP guidelines for infants receiving RV1 as opposed to RV5. The authors found that 83.3% of infants receiving RV1 and 76.4% of infants receiving RV5 were fully compliant with the ACIP vaccination schedule, and that 91.0% and 83.4% of infants receiving RV1 and RV5 completed the full vaccine series.(64)

Rotavirus vaccine effectiveness. Although the ACIP currently recommends both RV5 and RV1, RV1 may provide earlier protection than RV5 for fully vaccinated children and better overall protection for those receiving only one dose of vaccine because RV1 requires only two doses with the last dose given at age four months, while RV5 requires three doses with the last dose given at age six months.(65, 66) However, since the composition and

immune response mechanism of RV5 and RV1 differ, such arguments may not be fully justified. Unfortunately, since Phase III clinical trials of RV5 and RV1 used different methodologies, including different case definitions, follow-up times, and populations, comparative effectiveness analyses of the two rotavirus vaccines cannot be explored using clinical trial data.(65)

In the general US population, the rotavirus vaccines have been shown to be effective at reducing AGE and RGE among a variety of age groups and healthcare settings post-market.(67-80) A study of one-hundred percent hospital discharge data from 18 states participating in the Healthcare Cost and Utilization Project (HCUP) in 2007 and 2008 found reductions in AGE hospitalizations ranging from 28% to 50% across each of 8 age groups (0-2, 3-5, 6-11, 12-17, 18-23, 24-35, 36-47, 48-59 months), compared to the annual median rate of 101.1 hospitalizations per 10,000 children in the pre-rotavirus vaccine era, 2000-2006.(75) Reductions in AGE hospitalizations in age groups not eligible for rotavirus vaccination and when such vaccine coverage was low suggested that these vaccines may elicit robust herd protection. Another study using a cohort of commercially insured infants in the MarketScan Research Databases in the January-June period of 2008 and 2009 found a relative rate reduction of 89% (95% CI, 79 to 94) and 89% (95% CI, 84 to 93) in RGE hospitalizations among vaccinated versus unvaccinated infants.(76, 77) A case control study conducted at a large pediatric hospital in Houston, Texas in 2008 found that three doses of RV5 were 85% (95% CI, 55 to 95) and 89% (95% CI, 70 to 96) effective in preventing RGE hospitalizations and emergency department visits, and that completion of a partial series offered substantial protection.(77) In the outpatient setting, a study using an insurance claims database found that three doses of RV5 were 96% (95% CI, 76 to100) and 28% (95% CI, 22 to 33) effective

against RGE-coded and AGE-coded visits from January- May of 2007-2008.(79) Since the RV1 vaccine is still relatively new in the U.S., these studies have focused on the effectiveness of RV5, or have done so implicitly.

Two post-market studies have compared the effectiveness of RV5 and RV1 in the same or similar infant populations and found no difference in their effectiveness. However, one study had limited power, the other was an ecologic study, and neither was conducted in U.S. infants.(81, 82) Since herd immunity appears to be an important factor in post-market rotavirus vaccine effectiveness studies, effectiveness studies comparing RV5 and RV1 may be a challenge in geographic settings that administer both rotavirus vaccines (i.e., US from mid-2008 to present).

D. Synopsis or Summary

The rotavirus vaccines appear to have been highly effective in preventing RGE and AGE healthcare visits during the first few years post-licensure. Whether such high levels of effectiveness can be maintained, how much protection is attributable to direct versus indirect (herd) protection, how the effectiveness of RV5 compares to RV1, and how the effectiveness of a complete versus partial series compares deserve further exploration.

Only two studies have explored predictors of rotavirus vaccination, but since such exploration was not the main purpose of either study, a more thorough review of potential predictors are needed so targeted interventions can be developed. The current literature suggests that rotavirus vaccine coverage may be lower among non-Hispanic blacks compared to non-Hispanic whites and among infants visiting family physicians as opposed to pediatricians.

References

1. Halloran ME, Struchiner CJ, Longini IM,Jr. Study designs for evaluating different efficacy and effectiveness aspects of vaccines. Am J Epidemiol. 1997;146(10):789-803.

2. Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field. Further observations. Epidemiol Rev. 1988;10:212-41.

3. Schuchat A, Bell BP. Monitoring the impact of vaccines postlicensure: new challenges, new opportunities. Expert Rev Vaccines. 2008;7(4):437-56. (doi: 10.1586/14760584.7.4.437).

4. Dennehy PH. Acute diarrheal disease in children: epidemiology, prevention, and treatment. Infect Dis Clin North Am. 2005;19(3):585-602. (doi: 10.1016/j.idc.2005.05.003).

5. Wilhelmi I, Roman E, Sanchez-Fauquier A. Viruses causing gastroenteritis. Clin Microbiol Infect. 2003;9(4):247-62.

6. Parashar UD, Holman RC, Clarke MJ, et al. Hospitalizations associated with rotavirus diarrhea in the United States, 1993 through 1995: surveillance based on the new ICD-9-CM rotavirus-specific diagnostic code. J Infect Dis. 1998;177(1):13-7.

7. Malek MA, Curns AT, Holman RC, et al. Diarrhea- and rotavirus-associated hospitalizations among children less than 5 years of age: United States, 1997 and 2000. Pediatrics. 2006;117(6):1887-92. (doi: 10.1542/peds.2005-2351).

8. Charles MD, Holman RC, Curns AT, et al. Hospitalizations associated with rotavirus gastroenteritis in the United States, 1993-2002. Pediatr Infect Dis J. 2006;25(6):489-93. (doi: 10.1097/01.inf.0000215234.91997.21).

9. Glass RI, Kilgore PE, Holman RC, et al. The epidemiology of rotavirus diarrhea in the United States: surveillance and estimates of disease burden. J Infect Dis. 1996;174 Suppl 1:S5-11.

10. Cortes JE, Curns AT, Tate JE, et al. Trends in healthcare utilization for diarrhea and rotavirus disease in privately insured US children <5 years of age, 2001-2006. Pediatr Infect Dis J. 2009;28(10):874-8. (doi: 10.1097/INF.0b013e3181a653cd).

11. Pont SJ, Carpenter LR, Griffin MR, et al. Trends in healthcare usage attributable to diarrhea, 1995-2004. J Pediatr. 2008;153(6):777-82. (doi: 10.1016/j.jpeds.2008.06.037).

12. Torok TJ, Kilgore PE, Clarke MJ, et al. Visualizing geographic and temporal trends in rotavirus activity in the United States, 1991 to 1996. National Respiratory and Enteric Virus Surveillance System Collaborating Laboratories. Pediatr Infect Dis J. 1997;16(10):941-6.

13. Turcios RM, Curns AT, Holman RC, et al. Temporal and geographic trends of rotavirus activity in the United States, 1997-2004. Pediatr Infect Dis J. 2006;25(5):451-4. (doi: 10.1097/01.inf.0000214987.67522.78).

14. Centers for Disease Control and Prevention (CDC). Delayed onset and diminished magnitude of rotavirus activity--United States, November 2007-May 2008. MMWR Morb Mortal Wkly Rep. 2008;57(25):697-700.

15. Curns AT, Panozzo CA, Tate JE, et al. Remarkable postvaccination spatiotemporal changes in United States rotavirus activity. Pediatr Infect Dis J. 2011;30(1 Suppl):S54-5. (doi: 10.1097/INF.0b013e3181fefda9).

16. Staat MA, Azimi PH, Berke T, et al. Clinical presentations of rotavirus infection among hospitalized children. Pediatr Infect Dis J. 2002;21(3):221-7.

17. Desselberger U. Rotavirus infections: guidelines for treatment and prevention. Drugs. 1999;58(3):447-52.

18. Tate JE, Patel MM, Cortese MM, et al. Remaining issues and challenges for rotavirus vaccine in preventing global childhood diarrheal morbidity and mortality. Expert Rev Vaccines. 2012;11(2):211-20 (doi: 10.1586/erv.11.184).

19. Desai R, Esposito DH, Lees C, et al. Rotavirus-coded Deaths in Children, United States, 1999-2007. Pediatr Infect Dis J. 2011. (doi: 10.1097/INF.0b013e318220fe20).

20. Marshall GS. Rotavirus disease and prevention through vaccination. Pediatr Infect Dis J. 2009;28(4):355,62, quiz 363-4. (doi: 10.1097/INF.0b013e318199494a).

21. Murphy TV, Smith PJ, Gargiullo PM, et al. The first rotavirus vaccine and intussusception: epidemiological studies and policy decisions. J Infect Dis. 2003;187(8):1309-13. (doi: 10.1086/374420).

22. Centers for Disease Control and Prevention (CDC). Intussusception among recipients of rotavirus vaccine--United States, 1998-1999. MMWR Morb Mortal Wkly Rep. 1999;48(27):577-81.

23. Centers for Disease Control and Prevention (CDC). Suspension of rotavirus vaccine after reports of intussusception--United States, 1999. MMWR Morb Mortal Wkly Rep. 2004;53(34):786-9.

24. Bines JE, Patel M, Parashar U. Assessment of postlicensure safety of rotavirus vaccines, with emphasis on intussusception. J Infect Dis. 2009;200 Suppl 1:S282-90. (doi: 10.1086/605051).

25. Patel MM, Lopez-Collada VR, Bulhoes MM, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. N Engl J Med. 2011;364(24):2283-92. (doi: 10.1056/NEJMoa1012952).

26. Buttery JP, Danchin MH, Lee KJ, et al. Intussusception following rotavirus vaccine administration: Post-marketing surveillance in the National Immunization Program in Australia. Vaccine. 2011. (doi: 10.1016/j.vaccine.2011.01.088).

27. Perez-Vargas J, Isa P, Lopez S, et al. Rotavirus vaccine: early introduction in Latin America-risks and benefits. Arch Med Res. 2006;37(1):1-10. (doi: 10.1016/j.arcmed.2005.06.004).

28. Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med. 2006;354(1):23-33. (doi: 10.1056/NEJMoa052664).

29. Vesikari T, Karvonen A, Puustinen L, et al. Efficacy of RIX4414 live attenuated human rotavirus vaccine in Finnish infants. Pediatr Infect Dis J. 2004;23(10):937-43.

30. Vesikari T, Karvonen A, Prymula R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. Lancet. 2007;370(9601):1757-63. (doi: 10.1016/S0140-6736(07)61744-9).

31. Vesikari T, Itzler R, Matson DO, et al. Efficacy of a pentavalent rotavirus vaccine in reducing rotavirus-associated health care utilization across three regions (11 countries). Int J Infect Dis. 2007;11 Suppl 2:S29-35. (doi: 10.1016/S1201-9712(07)60019-8).

32. Block SL, Vesikari T, Goveia MG, et al. Efficacy, immunogenicity, and safety of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine at the end of shelf life. Pediatrics. 2007;119(1):11-8. (doi: 10.1542/peds.2006-2058).

33. Linhares AC, Velazquez FR, Perez-Schael I, et al. Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. Lancet. 2008;371(9619):1181-9. (doi: 10.1016/S0140-6736(08)60524-3).

34. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006;354(1):11-22. (doi: 10.1056/NEJMoa052434).

35. Parashar UD, Alexander JP, Glass RI, et al. Prevention of rotavirus gastroenteritis among infants and children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006;55(RR-12):1-13.

36. Cortese MM, Parashar UD, Centers for Disease Control and Prevention (CDC). Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2009;58(RR-2):1-25.

37. Kuehn BM. FDA: Benefits of rotavirus vaccination outweigh potential contamination risk. JAMA. 2010;304(1):30-1. (doi: 10.1001/jama.2010.863).

38. Centers for Disease Control and Prevention (CDC). National and state vaccination coverage among children aged 19--35 months --- United States, 2010. MMWR Morb Mortal Wkly Rep. 2011;60:1157-63.

39. Smith PJ, Humiston SG, Marcuse EK, et al. Parental delay or refusal of vaccine doses, childhood vaccination coverage at 24 months of age, and the Health Belief Model. Public Health Rep. 2011;126 Suppl 2:135-46.

40. Salmon DA, Smith PJ, Pan WK, et al. Disparities in preschool immunization coverage associated with maternal age. Hum Vaccin. 2009;5(8):557-61.

41. Cotter JJ, Bramble JD, Bovbjerg VE, et al. Timeliness of immunizations of children in a Medicaid primary care case management managed care program. J Natl Med Assoc. 2002;94(9):833-40.

42. Ponsonby AL, Couper D, Dwyer T, et al. Characteristics of infants receiving prompt first diphtheria-tetanus-pertussis immunisation in an infant cohort. Aust N Z J Public Health. 1997;21(5):489-94.

43. Rosenthal J, Rodewald L, McCauley M, et al. Immunization coverage levels among 19- to 35-month-old children in 4 diverse, medically underserved areas of the United States. Pediatrics. 2004;113(4):e296-302.

44. Centers for Disease Control and Prevention (CDC). National, state, and local area vaccination coverage among children aged 19-35 months --- United States, 2009. MMWR Morb Mortal Wkly Rep. 2010;59(36):1171-7.

45. Byrd KK, Santibanez TA, Chaves SS. Predictors of hepatitis A vaccination among young children in the United States. Vaccine. 2011;29(17):3254-9. (doi: 10.1016/j.vaccine.2011.02.028).

46. Williams IT, Milton JD, Farrell JB, et al. Interaction of socioeconomic status and provider practices as predictors of immunization coverage in Virginia children. Pediatrics. 1995;96(3 Pt 1):439-46.

47. Kum-Nji P, James D, Herrod HG. Immunization status of hospitalized preschool children: risk factors associated with inadequate immunization. Pediatrics. 1995;96(3 Pt 1):434-8.

48. Owen EC, Peddecord KM, Wang WW, et al. Hepatitis A vaccine uptake in San Diego County: Hispanic children are better immunized. Arch Pediatr Adolesc Med. 2005;159(10):971-6. (doi: 10.1001/archpedi.159.10.971).

49. Taylor JA, Darden PM, Slora E, et al. The influence of provider behavior, parental characteristics, and a public policy initiative on the immunization status of children followed by private pediatricians: a study from Pediatric Research in Office Settings. Pediatrics. 1997;99(2):209-15.

50. Zhao Z, Mokdad AH, Barker L. Impact of health insurance status on vaccination coverage in children 19-35 months old, United States, 1993-1996. Public Health Rep. 2004;119(2):156-62.

51. Bhatt P, Block SL, Toback SL, et al. A prospective observational study of US in-office pediatric influenza vaccination during the 2007 to 2009 influenza seasons: use and factors associated with increased vaccination rates. Clin Pediatr (Phila). 2010;49(10):954-63. (doi: 10.1177/0009922810370868).

52. Christakis DA, Mell L, Wright JA, et al. The association between greater continuity of care and timely measles-mumps-rubella vaccination. Am J Public Health. 2000;90(6):962-5.

53. McInerny TK, Cull WL, Yudkowsky BK. Physician reimbursement levels and adherence to American Academy of Pediatrics well-visit and immunization recommendations. Pediatrics. 2005;115(4):833-8. (doi: 10.1542/peds.2004-1510).

54. Poehling KA, Fairbrother G, Zhu Y, et al. Practice and child characteristics associated with influenza vaccine uptake in young children. Pediatrics. 2010;126(4):665-73. (doi: 10.1542/peds.2009-2620).

55. Stokley S, Smith PJ, Klevens RM, et al. Vaccination status of children living in rural areas in the United States: are they protected? Am J Prev Med. 2001;20(4 Suppl):55-60.

56. Smith PJ, Santoli JM, Chu SY, et al. The association between having a medical home and vaccination coverage among children eligible for the vaccines for children program. Pediatrics. 2005;116(1):130-9. (doi: 10.1542/peds.2004-1058).

57. Thomas M, Kohli V, King D. Barriers to childhood immunization: findings from a needs assessment study. Home Health Care Serv Q. 2004;23(2):19-39. (doi: 10.1300/J027v23n02_02).

58. Vannice KS, Salmon DA, Shui I, et al. Attitudes and beliefs of parents concerned about vaccines: impact of timing of immunization information. Pediatrics. 2011;127 Suppl 1:S120-6. (doi: 10.1542/peds.2010-1722R).

59. Smith PJ, Chu SY, Barker LE. Children who have received no vaccines: who are they and where do they live? Pediatrics. 2004;114(1):187-95.

60. Kempe A, Daley MF, Parashar UD, et al. Will pediatricians adopt the new rotavirus vaccine? Pediatrics. 2007;119(1):1-10. (doi: 10.1542/peds.2006-1874).

61. Kempe A, Patel MM, Daley MF, et al. Adoption of rotavirus vaccination by pediatricians and family medicine physicians in the United States. Pediatrics. 2009;124(5):e809-16. (doi: 10.1542/peds.2008-3832).

62. Kahane SM, Watt JP, Newell K, et al. Immunization levels and risk factors for low immunization coverage among private practices. Pediatrics. 2000;105(6):E73.

63. Patel MM, Clark AD, Glass RI, et al. Broadening the age restriction for initiating rotavirus vaccination in regions with high rotavirus mortality: benefits of mortality reduction versus risk of fatal intussusception. Vaccine. 2009;27(22):2916-22. (doi: 10.1016/j.vaccine.2009.03.016).

64. Krishnarajah G, Davis EJ, Fan Y, et al. Rotavirus vaccine series completion and adherence to vaccination schedules among infants in managed care in the United States. Vaccine. 2012;30(24):3717-22. (doi: 10.1016/j.vaccine.2011.12.077).

65. Toumi M, Vesikari T, Giaquinto C. Comment on the contribution by Weycker et al., "Cost of routine immunization of young children against rotavirus infection with Rotarix (R) versus RotaTeq (R)". Vaccine. 2010;28(45):7241; author reply 7242. (doi: 10.1016/j.vaccine.2010.08.086).

66. Weycker D, Sofrygin O, Kemner JE, et al. Cost of routine immunization of young children against rotavirus infection with Rotarix versus RotaTeq. Vaccine. 2009;27(36):4930-7. (doi: 10.1016/j.vaccine.2009.06.025).

67. Cortese MM, Tate JE, Simonsen L, et al. Reduction in gastroenteritis in United States children and correlation with early rotavirus vaccine uptake from national medical claims databases. Pediatr Infect Dis J. 2010;29(6):489-94. (doi: 10.1097/INF.0b013e3181d95b53).

68. Yen C, Tate JE, Wenk JD, et al. Diarrhea-associated hospitalizations among US children over 2 rotavirus seasons after vaccine introduction. Pediatrics. 2011;127(1):e9-e15. (doi: 10.1542/peds.2010-1393).

69. Begue RE, Perrin K. Reduction in gastroenteritis with the use of pentavalent rotavirus vaccine in a primary practice. Pediatrics. 2010;126(1):e40-5. (doi: 10.1542/peds.2009-2069).

70. Clark HF, Lawley D, Mallette LA, et al. Decline in cases of rotavirus gastroenteritis presenting to The Children's Hospital of Philadelphia after introduction of a pentavalent rotavirus vaccine. Clin Vaccine Immunol. 2009;16(3):382-6. (doi: 10.1128/CVI.00382-08).

71. Clark HF, Lawley D, Matthijnssens J, et al. Sustained decline in cases of rotavirus gastroenteritis presenting to the Children's Hospital of Philadelphia in the new rotavirus

vaccine era. Pediatr Infect Dis J. 2010;29(8):699-702. (doi: 10.1097/INF.0b013e3181d73524).

72. Payne DC, Staat MA, Edwards KM, et al. Direct and Indirect Effects of Rotavirus Vaccination Upon Childhood Hospitalizations in 3 US Counties, 2006-2009. Clin Infect Dis. 2011. (doi: 10.1093/cid/cir307).

73. Staat MA, Payne DC, Donauer S, et al. Effectiveness of Pentavalent Rotavirus Vaccine Against Severe Disease. Pediatrics. 2011;128(2):e267-75. (doi: 10.1542/peds.2010-3722).

74. Desai SN, Esposito DB, Shapiro ED, et al. Effectiveness of rotavirus vaccine in preventing hospitalization due to rotavirus gastroenteritis in young children in Connecticut, USA. Vaccine. 2010;28(47):7501-6. (doi: 10.1016/j.vaccine.2010.09.013).

75. Curns AT, Steiner CA, Barrett M, et al. Reduction in acute gastroenteritis hospitalizations among US children after introduction of rotavirus vaccine: analysis of hospital discharge data from 18 US states. J Infect Dis. 2010;201(11):1617-24. (doi: 10.1086/652403).

76. Cortes JE, Curns AT, Tate JE, et al. Rotavirus vaccine and health care utilization for diarrhea in U.S. children. N Engl J Med. 2011;365(12):1108-17. (doi: 10.1056/NEJMoa1000446).

77. Boom JA, Tate JE, Sahni LC, et al. Effectiveness of pentavalent rotavirus vaccine in a large urban population in the United States. Pediatrics. 2010;125(2):e199-207. (doi: 10.1542/peds.2009-1021).

78. Boom JA, Tate JE, Sahni LC, et al. Sustained protection from pentavalent rotavirus vaccination during the second year of life at a large, urban United States pediatric hospital. Pediatr Infect Dis J. 2010;29(12):1133-5. (doi: 10.1097/INF.0b013e3181ed18ab).

79. Wang FT, Mast TC, Glass RJ, et al. Effectiveness of the pentavalent rotavirus vaccine in preventing gastroenteritis in the United States. Pediatrics. 2010;125(2):e208-13. (doi: 10.1542/peds.2009-1246).

80. Tate JE, Cortese MM, Payne DC, et al. Uptake, impact, and effectiveness of rotavirus vaccination in the United States: review of the first 3 years of postlicensure data. Pediatr Infect Dis J. 2011;30(1 Suppl):S56-60. (doi: 10.1097/INF.0b013e3181fefdc0).

81. Martinon-Torres F, Alejandro MB, Collazo LR, et al. Effectiveness of rotavirus vaccination in Spain. Hum Vaccin. 2011;7(7).

82. Buttery JP, Lambert SB, Grimwood K, et al. Reduction in rotavirus-associated acute gastroenteritis following introduction of rotavirus vaccine into Australia's National Childhood vaccine schedule. Pediatr Infect Dis J. 2011;30(1 Suppl):S25-9. (doi: 10.1097/INF.0b013e3181fefdee).

CHAPTER II

STATEMENT OF SPECIFIC AIMS

A. Specific Aims, Hypotheses, and Rationale

In a population of US privately-insured infants and children,

1. Determine predictors of rotavirus vaccine initiation and completion

Hypothesis. We hypothesize that among ten available predictors, receipt of other childhood vaccines (diphtheria, tetanus, and acellular pertussis (DTaP) vaccines), the type of physician visited, and geographic size and density of infant residence will be the most important predictors of rotavirus vaccine series initiation and completion.

Rationale. Published studies have identified receipt of other childhood vaccines and physician type as important in predicting initiation or completeness of either the rotavirus vaccine series or other childhood vaccine series. We believe that parents and providers initiating rotavirus vaccination will generally ensure that the infant completes the series since individual and provider motivations and circumstances are unlikely to change during the short period of time between doses (two months). Certain geographic settings (rural areas) may be important predictors of both rotavirus vaccine series initiation and completion because access to a provider or the vaccine may be more difficult in these areas.

2. Assess timeliness of rotavirus vaccine administration as per the 2009 Advisory Committee on Immunization Practices (ACIP) guidelines

Hypothesis. The rotavirus vaccines will generally be administered as per the ACIP guidelines, but children vaccinated with monovalent rotavirus vaccine (RV1) will be more likely to complete the vaccine series than children vaccinated with pentavalent rotavirus vaccine (RV5).

Rationale. Since other childhood vaccinations are administered as recommended in the majority of populations studied, we expect most infants in our privately-insured population to be vaccinated according to the guidelines, especially since infants with health insurance may potentially have fewer problems accessing the health care system than other infant populations. However, since RV5 requires three doses, but RV1 requires just two doses to complete the series, we hypothesize that more infants will complete the RV1 series.

3. Estimate the direct, indirect, total, and overall rotavirus vaccine effectiveness (VE) against rotavirus gastroenteritis (RGE) and acute gastroenteritis (AGE) hospitalizations among those aged 8 to 20 months over the life course of the vaccines

Hypothesis. We hypothesize that the direct VE estimates will remain stable over time, but the indirect, total, and overall VE will generally increase.

Rationale. We expect herd protection to increase as the percentage of rotavirus-vaccinated children in the cohort increase. Since indirect VE is a measure of herd protection, and total and overall VE include measures of herd protection in their estimates, we expect these three measures of VE to increase over time.

4. Calculate the absolute rate reductions of RGE and AGE hospitalizations attributable to the rotavirus vaccine or the rotavirus vaccine program in those aged 8 to 20 months

   Hypothesis. Rate reductions of RGE and AGE hospitalizations will be underestimated when only direct or indirect effectiveness is considered.

   Rationale. Assuming that the direct VE of the rotavirus vaccines in our cohort is high (≥90%), accounting for indirect protection will increase the total VE of the vaccines only slightly since VE estimates cannot exceed 100%. However, the number of RGE and AGE hospitalizations prevented by indirect protection alone could still be large, and failing to account for indirect protection in rotavirus-vaccinated children could severely underestimate the impact of the rotavirus vaccine.

CHAPTER III

METHODS

A. Overview of Methods

Creating the various study cohorts required many steps. We were able to extract the outcome variables for both studies and our exposure variable for the VE study directly from the MarketScan Research Databases. However, many exposure variables for the patterns of use study and a few covariates for the VE study, including mother's age at infant birth, infant's primary provider type, and number siblings, had to be created using existing variables. Measurements of rurality required use of US Department of Agriculture (USDA) data. The infant's date of birth also had to be calculated indirectly using birthing codes. Our analysis used standard epidemiologic methods (log-risk regression, Cox proportional hazards regression).

B. Design

1. Subject Identification

a. Source Population

The MarketScan Commercial Claims and Encounters Database ("MarketScan Research Databases," Copyright © Thomson Truven Healthcare, Inc) served as the source population for both studies. Briefly, the MarketScan Research Databases link paid health insurance claims and encounter data to detailed patient information across sites, types of providers,

and over time.(1) From 2000 to 2010, the size of the database increased from approximately 68,000 to 920,000 infants. Since the infants and children in this database all have private insurance, they are not representative of the US population; however, they represent a large group of infants that may most commonly utilize the rotavirus vaccines.

b. Selection Criteria

Patterns of Use Analysis. Infants born in a hospital or outpatient setting between January 1, 2006 and September 30, 2010 were identified from the MarketScan Research Databases. We used the International Classification of Clinical Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for live born infants, V30-V39, to define the birth date of infants. If an infant had V30-V39 codes on multiple dates, the date of the first code was used as the birth date, and those without such codes and corresponding dates were excluded. Infants with birth dates occurring after administration of rotavirus vaccines, likely due to coding errors, were excluded.

For infants born between January 2006 and February 2010, additional eligibility criteria included having at least eleven months of continuous enrollment after birth. For infants born between March and September 2010, continuous enrollment was defined as enrollment at every month from birth until the end of the 2010 calendar year (the end of available data). In order to ensure adequate follow-up time, only infants born before March 2010 were included in assessments of vaccine series completion.

VE analysis. Infants with continuous enrollment during infancy, at least one outpatient record, and an ICD-9-CM birthing code (V30-V39) between May 1, 2000 and April 30, 2005 or May 1, 2006 and April 30, 2010 were abstracted from the databases. Birthing codes identified in mothers' claims were also used to identify birth dates of potentially eligible infants. If an infant or mother had a V30-V39 claim coded on multiple dates, the date of the first V30-V39 code was used as the birth date. Since follow-up for RGE began when infants turned eight months and continued until a maximum age of 20 months, infants receiving doses of rotavirus vaccine after age eight months were excluded so that rotavirus vaccine status could be treated as a time-independent variable.

Infants with commercial insurance failing to receive vaccines with high coverage rates (≥95%) may have differed from infants receiving such vaccines with respect to unmeasured confounding factors, so we required all infants in our study to be vaccinated with at least one dose of diphtheria, tetanus, and acellular pertussis vaccine (DTaP), using the following Current Procedural Terminology (CPT) codes: 90696, 90698, 90700, 90701, 90702, 90714, 90715, 90718, 90720, 90721, and 90723.

2. Methods for Proposed Study

a. Classification of Exposure

1. Exposure of Interest

Patterns of Use Analysis. We identified all potential predictors of rotavirus vaccination *a priori*. Individual level variables included sex, DTaP

vaccination status, number of siblings <10 years old, mother's age at birth, and hospitalizations prior to the first dose of rotavirus vaccine or by the maximum age at which the first dose of rotavirus vaccine could have been administered as per the ACIP guidelines (14 weeks, 6 days). Variables for race and socioeconomic status were not available.

Provider and health plan characteristics included the type of physician visited during ≥70% of the infant's outpatient visits (pediatrician, family physician, other providers, or no consistent provider type); the network of the care received during ≥70% of the infant's outpatient visits (in-network, or out-of-network or mixed); and the infant's type of health plan (basic, comprehensive, high-deductible; Exclusive Provider Organization (EPO) or Preferred Provider Organization (PPO); Health Maintenance Organization (HMO); Point of Service (POS) or POS with capitation ; or Consumer Directed Health Plan (CDHP)). All provider and health plan variables were assessed prior to rotavirus vaccination, or fifteen weeks of age if the infant was unvaccinated.

Our ecologic factors of interest were region of the infant's residence (Northeast, Midwest, South, or West) and rurality. In order to better measure rurality, we linked the US Department of Agriculture (USDA), Economic Research Service 2003 rural-urban continuum codes to the claims database via five-digit Federal Information Processing Standard (FIPS) codes. The 2003 rural-urban continuum codes distinguish metropolitan counties by the population size of the metropolitan area, and nonmetropolitan counties by the

population size, degree of urbanization, and adjacency to metropolitan areas. These codes classify every US County into either one of three metropolitan categories, or one of six nonmetropolitan categories.

VE Analysis. RV5 and RV1 vaccination status were identified using the Current Procedural Terminology codes (CPT) codes, 90680 and 90681, and treated as time-independent. To increase the specificity of vaccination status, we excluded infants living in states with state-funded rotavirus vaccine programs (Alaska, Idaho, Massachusetts, Maine, North Dakota, New Hampshire, New Mexico, Oregon, Rhode Island, Vermont, Washington, Wisconsin, and Wyoming).(2, 3)

2. Exposure Period

Patterns of Use Analysis. All infants meeting the inclusion were followed for evidence of rotavirus vaccination until their first birthday or the end of the study period (December 31, 2010), whichever came first. Predictors were examined and classified during the time period prior to administration of the first dose of rotavirus vaccine, or if no doses of rotavirus vaccine were administered, the maximum age at which the first dose of rotavirus vaccine could have been administered as per the 2009 ACIP guidelines (14 weeks, 6 days).

VE Analysis. The exposure, RV5 or RV1, was measured from birth up to the maximum age at which rotavirus vaccines are recommended (age 8 months, 0 days). Infants receiving a rotavirus vaccine after their 8 month birthday were excluded from the study because follow-up of RGE and AGE

began at age 8 months, and we chose to treat RV vaccine status as a time-independent variable. We followed infants and children from age eight months to the age at which they 1) experienced a RGE or AGE hospitalization; 2) lost continuous health plan enrollment; 3) reached their 20 month birthday; 4) reached the end of the study period, whichever happened first.

Infants and children were allowed to contribute person-time during two calendar years. For example, an infant turning eight months old on October 1, 2007, would contribute three person-months in 2007, and then re-enter the cohort on January 1, 2008 at age 11 months and contribute up to nine more calendar months of person-time in 2008.

3. Measurement Characteristics (reproducibility/validity)

The MarketScan Research Databases are available for purchase, and the details we provided in this dissertation as well as the manuscripts that will be submitted to peer-reviewed journals should allow our study to be reproduced by other researchers.

Internal validation was not possible because the MarketScan Research Databases are de-identified. To our knowledge, the exposures, outcomes, and covariates used in this study have not been validated by Thomson Truven Healthcare, Inc, the owners of the MarketScan Research Databases. However, these databases have fairly comprehensive coding. For example, diagnosis codes are found in 99% of all claims, procedure codes are found on

85% of physician claims and 100% of the claims are fully paid and adjudicated. (4) In the future, we plan to externally validate rotavirus vaccination status and RGE using the North Carolina Immunization Registry (NCIR) and the North Carolina Disease Event Tracking and Epidemiologic Research Tool (NC DETECT).

b. Classification of Outcome

Patterns of Use Analysis. For this analysis, our outcome was the exposure (rotavirus vaccination status) described for the VE analysis in Chapter III, Section 2a.

VE Analysis. Outcomes of RGE were identified using ICD-9-CM codes. Any of the 15 coding fields in the inpatient files of the databases was used to capture the ICD-9-CM code for rotavirus-specific disease, 008.61 Since rotavirus-coded events underestimate the true burden of rotavirus disease due to lack of routine laboratory testing and coding, we performed sensitivity analyses, assuming 25% and 50% sensitivity of the 008.61 code, and also abstracted and examined outcomes related to the following acute gastroenteritis (AGE) ICD-9-CM codes: bacterial (001-005, excluding 003.2, and also including 008.0-008.5), parasitic (006-007, excluding 006.3-006.6), and viral diarrhea (008.6 and 008.8); diarrhea of undetermined etiology (presumed infectious [009.0-009.3] and presumed noninfectious [558.9]); and diarrhea not otherwise specified (787.91). (6-9)

3. Data Analysis

For both studies, data were analyzed in SAS, version, 9.2 (SAS Institute, Inc).

Patterns of Use Analysis. We calculated simple frequencies, and performed bivariate and multivariable regression analyses using log-risk models that were limited to individual, provider, and ecological characteristics thought to be associated with receipt of at least one dose of rotavirus vaccine, and identifiable in the available data. We also used the same potential individual, provider, and ecological characteristics to explore predictors of rotavirus vaccine series completion. In order to examine whether predictors of rotavirus vaccination changed over time, we repeated the above analyses, restricting the cohort to infants born in 2006 and then 2009. Infants with missing data on any potential predictors were excluded from both of these analyses.

VE Analysis. We used Cox proportional hazard regression models to calculate hazard rate ratios, comparing the hazard of RGE or AGE hospitalization among vaccinated infants to unvaccinated infants entering the cohort in 2007, 2008, 2009, or 2010 and subtracting the result from one to obtain direct VE estimates by calendar year. We similarly calculated the indirect, total, and overall VE, varying the comparison cohorts as appropriate. For indirect VE, we compared unvaccinated infants followed during each calendar year of the rotavirus vaccine period, 2007-2010, to (unvaccinated) infants followed during the baseline period, 2001-2005. For total VE, we compared vaccinated infants followed during each calendar year of the rotavirus vaccine period to (unvaccinated) infants followed during the baseline period. For overall or average VE, we compared all vaccinated and unvaccinated infants during each calendar year of the rotavirus vaccine period to (unvaccinated) infants followed during the baseline period. Results were stratified by year to account

for increasing vaccination coverage and adjusted for month of birth to account for the seasonality of rotavirus virus.

Incidence rate differences based on the case count and person-years in our population, and additional analyses assuming 25% and 50% sensitivity and 100% specificity of the RGE and AGE ICD-9-CM codes were calculated to determine the absolute number of RGE and AGE hospitalizations prevented by the rotavirus vaccine program in our cohort.

References

1. MarketScan Database, Thomson Reuters (Healthcare) Inc. MarketScan User Guide Commercial Claims and Encounters Medicare Supplemental and Coordination of Benefits, Data Year 2007 Edition. , 2008.

2. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol. 2005;58(4):323-37. (doi: 10.1016/j.jclinepi.2004.10.012).

3. Cortes JE, Curns AT, Tate JE, et al. Rotavirus vaccine and health care utilization for diarrhea in U.S. children. N Engl J Med. 2011;365(12):1108-17. (doi: 10.1056/NEJMoa1000446).

4. Adamson DM, Chang S, Hansen LG. Health Research Data for the Real World: The MarketScan Databases. , 2008.

5. Hsu VP, Staat MA, Roberts N, et al. Use of active surveillance to validate international classification of diseases code estimates of rotavirus hospitalizations in children. Pediatrics. 2005;115(1):78-82. (doi: 10.1542/peds.2004-0860).

6. Patel MM, Tate JE, Selvarangan R, et al. Routine laboratory testing data for surveillance of rotavirus hospitalizations to evaluate the impact of vaccination. Pediatr Infect Dis J. 2007;26(10):914-9. (doi: 10.1097/INF.0b013e31812e52fd).

7. Desai R, Curns AT, Steiner CA, et al. All-cause gastroenteritis and rotavirus-coded hospitalizations among US children, 2000-2009. Clin Infect Dis. 2012;55(4):e28-34. (doi: 10.1093/cid/cis443).

8. Cortes JE, Curns AT, Tate JE, et al. Trends in healthcare utilization for diarrhea and rotavirus disease in privately insured US children <5 years of age, 2001-2006. Pediatr Infect Dis J. 2009;28(10):874-8. (doi: 10.1097/INF.0b013e3181a653cd).

CHAPTER IV

RESULTS

A. Patterns of rotavirus vaccine uptake and use in privately-insured US infants, 2006-2010

1. Introduction

Rotavirus gastroenteritis is a leading cause of hospitalizations and emergency department visits among young children in the US.(1) The recently licensed rotavirus vaccines, RotaTeq® (Rotavirus Vaccine, live, oral, pentavalent) [RV5] (Merck & Co., Inc.) and Rotarix® (Rotavirus Vaccine, live, oral, monovalent) [RV1] (GlaxoSmithKline Biologicals), have dramatically reduced incidence of healthcare utilization for rotavirus infection.(2) These vaccines are now recommended for routine use among US infants by the Advisory Committee on Immunization Practices (ACIP).(3, 4)

Despite these recommendations, the Centers for Disease Control and Prevention (CDC) estimated that only 67% of eligible children 19-35 months in the US had completed a rotavirus vaccine series in 2011.(5) Among nine recommended pediatric vaccines assessed by the National Immunization Survey (NIS) in 2011, only the hepatitis A vaccine had lower coverage than the rotavirus vaccine in the US.(5) Little is known about why it can take several years or more for newly recommended vaccines like the rotavirus vaccine to reach high coverage levels, but studies to-date

suggest that type of physician visited, geographic residence, socio-economic status, and race may be important predictors.(5-8) Considering that the US Department of Health and Human Services (HHS) Healthy People 2020 objectives include vaccinating at least 80% of children with two or more doses of rotavirus vaccine by 2020, further exploration regarding the determinants of rotavirus vaccine uptake is warranted.(9)

Using data from a large population of infants with commercial insurance, we study patterns of use of rotavirus vaccine. We examine individual, provider, and ecologic correlates of rotavirus vaccine use and vaccine series completion. We hypothesize that receipt of other childhood vaccines (e.g., diphtheria, tetanus, and acellular pertussis (DTaP) vaccines) and the type of physician visited will be the most important predictors of rotavirus vaccine series initiation and completion. Our study further examines time trends and timeliness of rotavirus vaccine administration as per the 2009 ACIP recommendations.

2. Methods

Infants born in a hospital or outpatient setting between January 1, 2006 and September 30, 2010 were identified from the MarketScan Research Databases (Copyright © Thomson Truven Healthcare, Inc). We used the International Classification of Clinical Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for live born infants, V30-V39, to define the birth date of infants. If an infant had V30-V39 codes on multiple dates, the date of the first code was used as the birth date, and those without such codes and corresponding dates were excluded.

Infants with birth dates occurring after administration of rotavirus vaccines, likely due to coding errors, were excluded.

For infants born between January 2006 and February 2010, additional eligibility criteria included having at least eleven months of continuous enrollment after birth. For infants born between March and September 2010, continuous enrollment was defined as enrollment at every month from birth until the end of the 2010 calendar year (the end of available data). In order to ensure adequate follow-up time, only infants born before March 2010 were included in assessments of vaccine series completion.

RV5 and RV1 vaccination status was assessed using the Current Procedural Terminology (CPT) codes, 90680 and 90681. We required infants to have at least one outpatient claim because we thought it was important for our cohort to include only infants that utilized the healthcare system through their private insurance plan to reduce potential misclassification of rotavirus vaccination status. To further reduce exposure misclassification, we excluded infants residing in 13 states with state-funded vaccine programs (Alaska, Idaho, Massachusetts, Maine, North Dakota, New Hampshire, New Mexico, Oregon, Rhode Island, Vermont, Washington, Wisconsin, and Wyoming) except for the cohort of infants used to examine adherence to the recommended vaccine schedule.(2)

We used the 2009 ACIP recommendations to assess adherence to the recommended rotavirus vaccine schedule for all calendar years, 2006-2010. If the first dose of rotavirus vaccine was given before the age of six weeks, zero days or after the age of fourteen weeks, six days, then the recommendations were not met.

We also considered recommendations to have been violated if any dose was given after the age of eight months, zero days, or if the minimum interval between two doses was less than four weeks.

We calculated simple frequencies, and performed bivariate and multivariable regression analyses using log-risk models that were limited to individual, provider, and ecological characteristics thought to be associated with receipt of at least one dose of rotavirus vaccine, and identifiable in the available data. We also used the same potential individual, provider, and ecological characteristics to explore predictors of rotavirus vaccine series completion. In order to examine whether predictors of rotavirus vaccination changed over time, we repeated the above analyses, restricting the cohort to infants born in 2006 and then 2009. Infants with missing data on any potential predictors were excluded from both of these analyses.

We identified all potential predictors of rotavirus vaccination *a priori*. Individual level variables included sex, DTaP vaccination status, number of siblings <10 years old, mother's age at birth, and hospitalizations prior to the first dose of rotavirus vaccine or by the maximum age at which the first dose of rotavirus vaccine could have been administered as per the ACIP guidelines (14 weeks, 6 days). Variables for race and socioeconomic status were not available. Provider and health plan characteristics included the type of physician visited during ≥70% of the infant's outpatient visits (pediatrician, family physician, other providers, or no consistent provider type); the network of the care received during ≥70% of the infant's outpatient visits (in-network, or out-of-network or mixed); and the infant's type of health plan (basic, comprehensive, high-deductible; Exclusive Provider Organization

(EPO) or Preferred Provider Organization (PPO); Health Maintenance Organization (HMO); Point of Service (POS) or POS with capitation; or Consumer Directed Health Plan (CDHP)). All provider and health plan variables were assessed prior to rotavirus vaccination, or fifteen weeks of age if the infant was unvaccinated. Our ecologic factors of interest were region of the infant's residence (Northeast, Midwest, South, or West) and rurality. In order to better measure rurality, we linked the US Department of Agriculture (USDA), Economic Research Service 2003 rural-urban continuum codes to the claims database via five-digit Federal Information Processing Standard (FIPS) codes. The 2003 rural-urban continuum codes distinguish metropolitan counties by the population size of the metropolitan area, and nonmetropolitan counties by the population size, degree of urbanization, and adjacency to metropolitan areas. These codes classify every US County into either one of three metropolitan categories, or one of six nonmetropolitan categories.

All data were managed and analyzed in SAS, version 9.2 (SAS Institute, Cary, NC). This study was considered exempt from human subjects review by the institutional review board at the University of North Carolina.

3. Results

Infant cohorts. Approximately half (51%) of 2.80 million infants identified in the enrollment files between January 2006 and December 2010 had an identifiable ICD-9 birthing code and corresponding date of service (Figure 3). Infants that were excluded due to missing data generally lacked information on their mother's age at birth. After additional exclusions, our final cohorts to assess

predictors of rotavirus vaccine initiation and completion included 594,117 and 324,264 infants, respectively.

Temporal trends of rotavirus vaccine uptake. Rotavirus vaccine uptake among infants in our cohort increased from 0% when RV5 was licensed (February 2006) to 25% when the first ACIP recommendations were published (August 2006) (Figure 1). Rotavirus vaccine uptake then increased even more rapidly, doubling to 49% by December 2006. The percentage of infants receiving at least one dose of rotavirus vaccine continued to grow steadily, reaching 62% by April 2007 and reaching 70% beginning November 2007. Throughout 2009 and 2010, a median of 81% (range, 78%-83%) of eligible infants were vaccinated with at least one dose of rotavirus vaccine each month. Among the infants receiving a rotavirus vaccine during our study period, 92% received RV5, 5% received RV1, and 3% received a combination of the two vaccines.

Adherence to the 2009 ACIP recommendations. The median and inter-quartile range of ages at which infants received doses of rotavirus vaccine followed the 2009 ACIP guidelines of two, four, and six months of age (Table 1). Almost all infants received their rotavirus vaccines between the minimum (6 weeks) and maximum (8 months, 0 days) recommended ages, and received dose one and dose two at least four weeks apart. Although the 2009 ACIP guidelines do not specify a maximum interval in which two doses should be given, 18% of infants received a second dose of rotavirus vaccine more than 10 weeks after their first dose, and 7% of infants received their second dose more than 12 weeks after their first dose. Across all years, approximately 8% of infants received their first dose of rotavirus vaccine at

ages older than the maximum recommended age for the first dose (14 weeks, 6 days), with 19% of infants in 2006 and 6.0-8.5% of infants from 2007 to 2010, receiving their first dose after age 14 weeks, 6 days. Although most infants who initiated rotavirus vaccination completed the full series, more infants completed the series for RV1 than RV5 or a combination of the two vaccines (87% versus 79% versus 73%, P<0.001).

Univariate, bivariate and multivariable analyses. Among 594,117 infants, 69% received at least one dose of rotavirus vaccine between February 2006 and December 2010 (Table 2). Most infants in the cohort were also vaccinated with at least one dose of DTaP, were born to mothers 25-39 years of age, were first born children or had one older sibling, visited in-network physicians, were enrolled in EPO or PPO health plans, received outpatient care from pediatricians, resided in the Midwest or South, and lived in large metropolitan areas.

The strongest predictors of rotavirus vaccine initiation among infants born January 2006-September 2010 were receipt of DTaP (bivariate: RR= 7.91, 95% CI= 7.69-8.13; multivariable: RR= 7.50, 95% CI= 7.30-7.71), and visiting a pediatrician versus family physician for routine care (bivariate: RR= 1.64, 95% CI= 1.63-1.66; multivariable: RR=1.51, 95% CI=1.49-1.52). Infants were slightly less likely to receive a rotavirus vaccine if they lived in the Northeast as opposed to the South, or in a small urban or rural area as opposed to a large metropolitan area. As the number of siblings less than 10 years of age in the household increased, infants became less likely to receive a rotavirus vaccine.

In order to determine whether predictors of rotavirus vaccine initiation changed over time, we also examined predictors of infants born when RV5 was first licensed (2006) with those born three years after RV5 licensure (2009). Compared to the 2006 birth cohort, visiting a pediatrician versus a family physician in the 2009 birth cohort was a less important predictor of rotavirus vaccine initiation (2006: RR=2.15, 95% CI= 2.02-2.28; 2009: RR=1.35, 95% CI = 1.32-1.37) as was residing in a metropolitan area with less than one million population versus an area with at least one million population.

Family physicians often provide care more frequently in rural areas, and infants visiting family physicians or residing in rural areas were independently less likely to receive a dose of rotavirus vaccine. We therefore explored potential interactions between the type of physician visited (pediatrician versus family physician) for routine care and population size of residence (metropolitan areas versus non-metropolitan areas), but did not find an interaction in these post-hoc analyses (Figure 2).

The most important predictors of rotavirus vaccine series completion were receipt of DTaP and receiving routine care from a pediatrician as opposed to a family physician. The strength of the associations in multivariable analyses were 6-fold and 1.3-fold smaller than in the multivariable analyses of rotavirus vaccine initiation, and the strength of the association decreased from 2006 to 2009 (Table 3). Infants born to younger mothers (<25 years) and with more siblings were slightly less likely to complete the rotavirus vaccine series, and this trend remained consistent in 2006 and 2009. Infants residing outside of metropolitan areas were generally less likely to

complete the rotavirus vaccine series. Region of residence was not an important predictor of vaccine series completion.

4. Discussion

We observed rapid diffusion of the rotavirus vaccine into routine practice shortly after licensure in the US. Approximately three quarters of infants born from early 2008 through mid-2010, received two or more doses. This estimate is slightly higher than the CDC estimate that analyzed data for infants born during approximately the same time period using a population-based telephone survey (NIS), and 5% lower than the HHS' Healthy People 2020 goal.(5, 9) Our estimate may be higher than the CDC estimate and may have overestimated the progress towards the Healthy People 2020 goal for several reasons. First, our population included only infants with commercial insurance who may be more likely to be vaccinated than other infant populations, such as the uninsured or those with Medicaid insurance. Second, our cohort consisted of a non-population based sample of infants. Since the MarketScan Research Databases have increased in size over time, our data were weighted towards the later years (e.g., 2010) when rotavirus vaccine coverage was relatively high compared to the earlier years. In addition, infants residing in rural and small urban areas were less likely to be vaccinated in our study, but also underrepresented.

It was surprising that one-quarter of eligible infants received at least one dose of rotavirus vaccine prior to the publication of the first ACIP recommendations in August 2006. This reflects the importance of other communication networks and the apparent readiness of the manufacturer, insurance companies, and providers to deliver the rotavirus vaccine. Despite the initial rapid uptake of the rotavirus vaccine,

approximately one-fifth of infants were still not receiving the vaccine in January 2009 and coverage has failed to further increase since this time. Education interventions, particularly those targeted at family physicians should be considered. This recommendation is consistent with the results of a 2007 nationally-representative survey of pediatricians and family physicians which found that pediatricians were much more likely to administer the rotavirus vaccine to eligible infants than family physicians, possibly because family physicians were more concerned with vaccine safety and adding additional vaccines to the childhood schedule than pediatricians.(8) Studies examining other vaccines in various populations of infants and young children have also shown that family physicians may be less likely to adopt and may be less knowledgeable about vaccine recommendations than pediatricians.(10)

Since most children who received a rotavirus also received at least one other recommended childhood vaccine (e.g., DTaP), it appears that neither parents nor providers are "cherry-picking" vaccines. Rather, it appears that infants either generally receive the recommended childhood vaccines or do not. This observation is further supported by a post-hoc analysis that found a high correlation between the number of doses of DTaP (one, two, or three) and number of doses of RV5 (one, two, or three) received among infants in our cohort ($r=0.76$). Since our cohort consisted of infants with private insurance who had at least one outpatient record, failure to access the healthcare system cannot fully explain why some infants did not receive recommended vaccines, such as DTaP or rotavirus. Based on our results, interventions aimed at increasing the coverage of any one childhood vaccine may help increase the coverage and timeliness of other recommended childhood vaccines,

assuming that vaccine availability is not an issue. This was shown to be the case for the DTaP vaccine in Australia, where the third dose coverage of DTaP vaccine in a pre-RV5 cohort was 80%, but increased by 5 to 12 percent once the RV5 vaccine was available and widely used.(11)

Overall, adherence to the 2009 ACIP guidelines for rotavirus vaccine administration was high. Although we compared all years of data (2006 to 2010) to the 2009 ACIP guidelines which are less stringent than the 2006 ACIP guidelines, adherence remained high even when we reanalyzed our data using the 2006 ACIP guidelines (data not shown). Despite overall high levels of compliance to the 2009 ACIP recommendations, ensuring that infants complete the rotavirus vaccine series could be improved. Other multi-dose vaccines face a similar challenge. Prior to rotavirus vaccine availability, the vaccination histories of over 17,000 children in the 2005 NIS were reviewed, revealing that of the 28% of children not compliant with ACIP recommendations, two-thirds were categorized as such because they were missing doses for multi-dose vaccinations.(12) However, since vaccination coverage has been shown to increase as the number of physician office visits increase, one remedy physicians could consider is vaccinating infants at-risk for missing office visits with RV1 since it requires only two doses to complete the series.(13) However, since identifying infants at-risk for missing office visits can be difficult, this recommendation may only be practical in theory. Furthermore, post-marketing data comparing partial series effectiveness of RV5 to RV1 are limited.(14)

Our analyses are subject to limitations. Many variables potentially predictive of rotavirus vaccine uptake were not available in our data. Further research is needed to examine the effect of potentially relevant predictors, such as race, ethnicity, family economic status, and physician reimbursement levels. We were unable to validate important estimated dates, such as birth dates and rotavirus vaccination dates. While such misclassifications could affect the results of our analysis that assesses adherence to the 2009 ACIP recommendations, we do not suspect that there was enough misclassification to affect our overall conclusions and they are consistent with the results from another recently published study.(15) As mentioned earlier in the discussion, the infants in our cohorts were not representative of the US infant population; however, our study included nearly 600,000 infants with commercial insurance who may represent the group of infants that most commonly utilizes the rotavirus vaccines.

Our study revealed rapid initial uptake of the vaccine after RV5 was first licensed. However, even several years after licensure, many children still did not receive the vaccine or received an incomplete series. Quality improvement efforts should focus on ensuring that (1) infants complete the two-dose series for RV1 and three-dose series for RV5 or a mixed series; (2) family physicians receive the adequate education and support necessary to increase the rates of vaccination among infants in their care; and (3) other recommended infant vaccinations are administered.

5. Figures and Tables

FIGURE 1. Percent and number of infants vaccinated with at least one dose of rotavirus vaccine, February 2006-November 2010 (n=825,300)

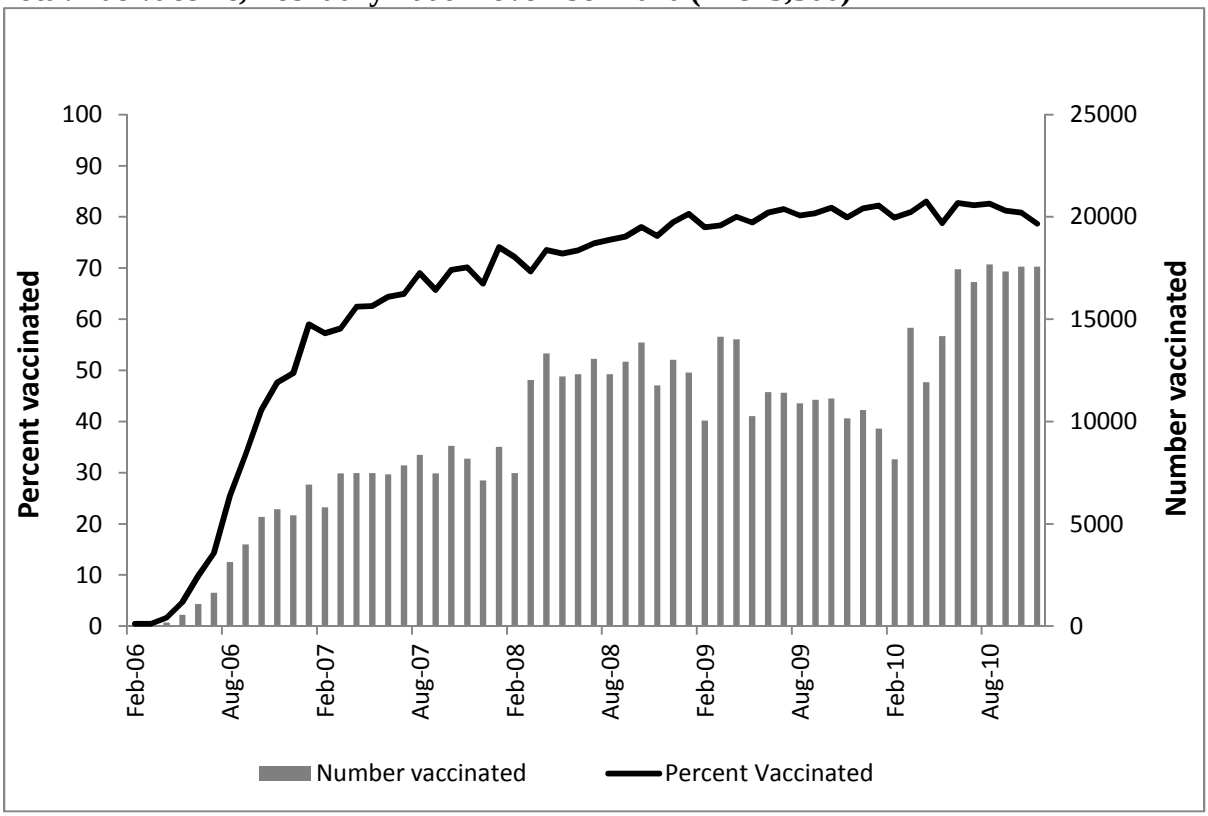


TABLE 1. Adherence to the rotavirus vaccination 2009 ACIP Guidelines (n=486,295)[1]

Variable	Number (%)	
Median age in days (IQR)		
Dose 1	63	(61-69)
Dose 2	126	(123-135)
Dose 3 (RV5 only)	188	(184-197)
RV5, number of doses received in series		
One (incomplete)	30,256	(6.8)
Two (incomplete)	63,294	(14.2)
Three (complete)	349,599	(78.4)
Four or more (too many doses)	2589	(0.6)
RV1, number of doses received in series		
One (incomplete)	3509	(13.5)
Two (complete)	21,588	(83.3)
Three or more (too many doses)	823	(3.2)
Mixed series		
Incomplete	3933	(26.9)
Complete	9819	(67.1)
Complete (too many doses)	885	(6.1)
Administered first dose too early (<6 weeks)		
No	484,979	(99.7)
Yes	1316	(0.3)
Administered first dose too late (>14 weeks, 6 days)		
No	447,442	(92.0)
Yes	39,557	(8.0)
Administered any dose too late (>8 months, 0 days)		
No	476,647	(98.0)
Yes	9648	(2.0)
Minimum interval between first two doses violated (<4 weeks)		
No	450,922	(99.6)
Yes	1608	(0.4)

[1]Infants vaccinated with RV5, RV1, or a mixed series and enrolled ≥11months.
Abbreviations: ACIP, Advisory Committee on Immunization Practices; IQR, interquartile range; RV1, monovalent rotavirus vaccine; RV5, pentavalent rotavirus vaccine

TABLE 2. Estimates of rotavirus vaccine receipt, one or more doses (n=594,117)

Variable	No. infants receiving ≥1 dose of RV5 or RV1 in category, born 2006-2010 (%)	Bivariate RR, born 2006-2010 (95% CI)	Multivariable RR, born 2006-2010 (95% CI)	Multivariable RR, born 2006 (95% CI)	Multivariable RR, born 2009 (95% CI)
Overall	409,557 (68.9)	---	---	---	---
Sex					
Female	200,442 (69.0)	Ref	Ref.	Ref.	Ref.
Male	209,115 (68.9)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.98-1.02)	1.00 (1.00-1.00)
DTaP vaccination					
No	4645 (9.4)	Ref	Ref.	Ref.	Ref.
Yes	404,912 (74.3)	7.91 (7.69-8.13)	7.50 (7.30-7.71)	7.28 (6.59-8.04)	6.95 (6.57-7.34)
Hospitalized					
No	397,832 (69.1)	Ref	Ref.	Ref.	Ref.
Yes	11,725 (64.3)	0.93 (0.92-0.94)	0.96 (0.95-0.97)	1.05 (1.00-1.10)	0.99 (0.98-1.00)
Number of siblings <10 years					
0	187,647 (71.2)	Ref	Ref.	Ref.	Ref.
1	156,922 (68.7)	0.96 (0.96-0.97)	0.97 (0.97-0.97)	0.96 (0.94-0.98)	0.99 (0.98-0.99)
2	52,803 (64.9)	0.91 (0.91-0.92)	0.94 (0.94-0.94)	0.95 (0.92-0.97)	0.97 (0.96-0.97)
3 or more	12,185 (58.3)	0.81 (0.81-0.83)	0.89 (0.88-0.90)	0.91 (0.86-0.96)	0.90 (0.88-0.91)
Mother's age (years)					
<25	36,376 (63.7)	0.91 (0.90-0.91)	0.95 (0.95-0.96)	0.96 (0.93-0.99)	0.99 (0.98-1.00)
25-<30	130,089 (68.9)	0.98 (0.97-0.98)	0.99 (0.99-0.99)	0.98 (0.96-1.00)	1.00 (1.00-1.00)
30-<35	152,610 (70.4)	Ref	Ref.	Ref.	Ref.
35-40	75,185 (69.2)	0.98 (0.98-0.99)	0.99 (0.98-0.99)	1.02 (0.99-1.05)	0.99 (0.99-1.00)
≥40	15,297 (67.5)	0.96 (0.95-0.97)	0.97 (0.97-0.98)	0.95 (0.90-1.00)	0.98 (0.97-0.99)
Primary provider type					
Pediatrician	266,740 (75.8)	1.64 (1.63-1.66)	1.51 (1.49-1.52)	2.15 (2.02-2.28)	1.35 (1.32-1.37)
Family physician	15,790 (46.1)	Ref.	Ref.	Ref.	Ref.

Other providers	75,312 (61.3)	1.33 (1.31-1.34)	1.31 (1.29-1.32)	1.77 (1.66-1.88)	1.27 (1.25-1.30)
No consistent provider type	51,715 (60.6)	1.31 (1.30-1.33)	1.30 (1.28-1.32)	1.53 (1.43-1.64)	1.23 (1.21-1.26)
Network of provider type					
In-network	368,525 (69.4)	1.07 (1.07-1.08)	1.00 (1.00-1.00)	0.91 (0.88-0.94)	0.99 (0.98-1.00)
Out of network or mix of networks	41,032 (64.7)	Ref.	Ref.	Ref.	Ref.
Health plan type					
Basic, comprehensive, or high deductible	7597 (68.0)	0.99 (0.98-1.01)	1.02 (1.01-1.03)	0.76 (0.70-0.83)	1.01 (0.99-1.03)
EPO or PPO	293,141 (68.6)	Ref.	Ref.	Ref.	Ref.
HMO	59,901 (70.5)	1.03 (1.02-1.03)	0.99 (0.98-0.99)	0.90 (0.88-0.93)	1.00 (0.99-1.01)
POS or POS with capitation	36,495 (68.5)	1.00 (0.99-1.01)	0.97 (0.96-0.97)	0.98 (0.95-1.01)	1.00 (0.99-1.01)
CDHP	12,423 (72.9)	1.06 (1.05-1.07)	1.03 (1.02-1.04)	0.95 (0.90-1.01)	1.01 (0.99-1.01)
Region of residence					
Northeast	48,468 (68.2)	0.96 (0.95-0.96)	0.92 (0.92-0.93)	0.73 (0.70-0.76)	0.89 (0.89-0.90)
Midwest	122,396 (66.0)	0.93 (0.92-0.93)	0.98 (0.98-0.98)	0.94 (0.92-0.96)	1.01 (1.01-1.02)
South	202,587 (71.3)	Ref.	Ref.	Ref.	Ref.
West	36,106 (67.9)	0.95 (0.95-0.96)	0.97 (0.97-0.98)	0.72 (0.69-0.76)	0.97 (0.96-0.98)
Type of residence					
Metro with ≥1 M pop	250,066 (71.2)	Ref.	Ref.	Ref.	Ref.
Metro with 250,000 – 1 M pop	74,009 (70.3)	0.99 (0.98-0.99)	1.04 (1.03-1.04)	1.16 (1.13-1.19)	1.02 (1.01-1.02)
Metro with <250,000 pop	39,238 (67.8)	0.95 (0.95-0.96)	1.01 (1.00-1.02)	1.20 (1.16-1.23)	1.00 (0.99-1.01)
Urban with ≥20,000 pop, adjacent to metro area	13,445 (61.9)	0.87 (0.86-0.88)	0.98(0.97-0.99)(	1.02 (0.97-1.07)	0.98 (0.96-0.99)
Urban with ≥20,000 pop, not adjacent to metro area	6348 (56.8)	0.80 (0.78-0.81)	0.93 (0.92-0.94)	0.99 (0.92-1.06)	0.96 (0.94-0.98)
Urban with 2500-19,999 pop, adjacent to metro area	15,416 (58.5)	0.82 (0.81-0.83)	0.96 (0.95-0.97)	0.95 (0.91-1.00)	0.96 (0.94-0.97)
Urban with 2500-19,999 pop, not adjacent to metro area	7048 (50.5)	0.71 (0.70-0.72)	0.90 (0.89-0.92)	0.91 (0.84-0.97)	0.94 (0.92-0.96)
Rural or <2500 population, adjacent to metro area	2146 (63.7)	0.89 (0.87-0.92)	0.99 (0.97-1.01)	1.01 (0.90-1.15)	0.99 (0.96-1.02)

Rural or <2500 population, not adjacent to metro area	1841 (56.1)	0.79 (0.76-0.81)	0.98 (0.95-1.00)	1.04 (0.90-1.20)	0.94 (0.90-0.98)

Abbreviations: CDHP, Consumer Directed Health Plan; DTaP, diphtheria, tetanus, and acellular pertussis; EPO, Exclusive Provider Organization; HMO, Health Maintenance Organization; Metro, metropolitan; Pop, population; POS, Point of Service; PPO, Preferred Provider Organization; RV1, monovalent rotavirus vaccine; RV5, pentavalent rotavirus vaccine

FIGURE 2. Percent of infants vaccinated with at least one dose of rotavirus vaccine, February 2006-November 2010 by physician type and geographic area[1] (n=385,291)

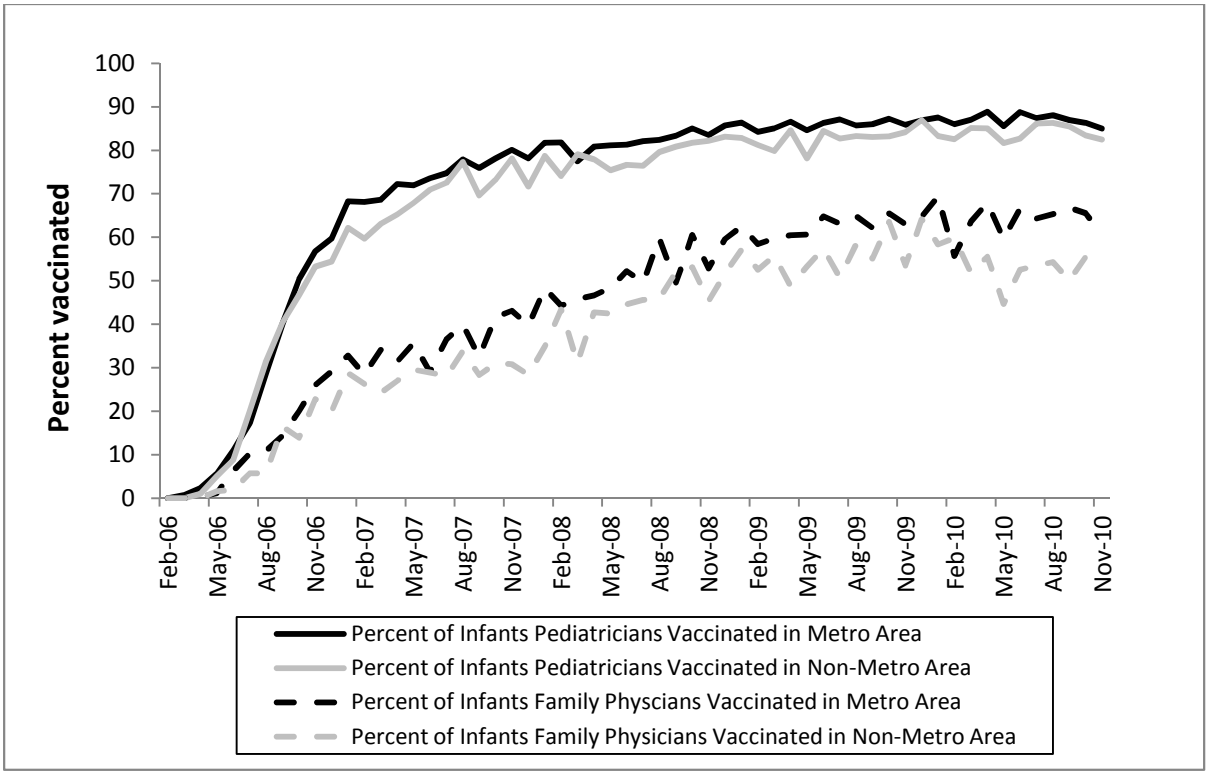


TABLE 3. Estimates of rotavirus vaccine series completion (n=324,264)

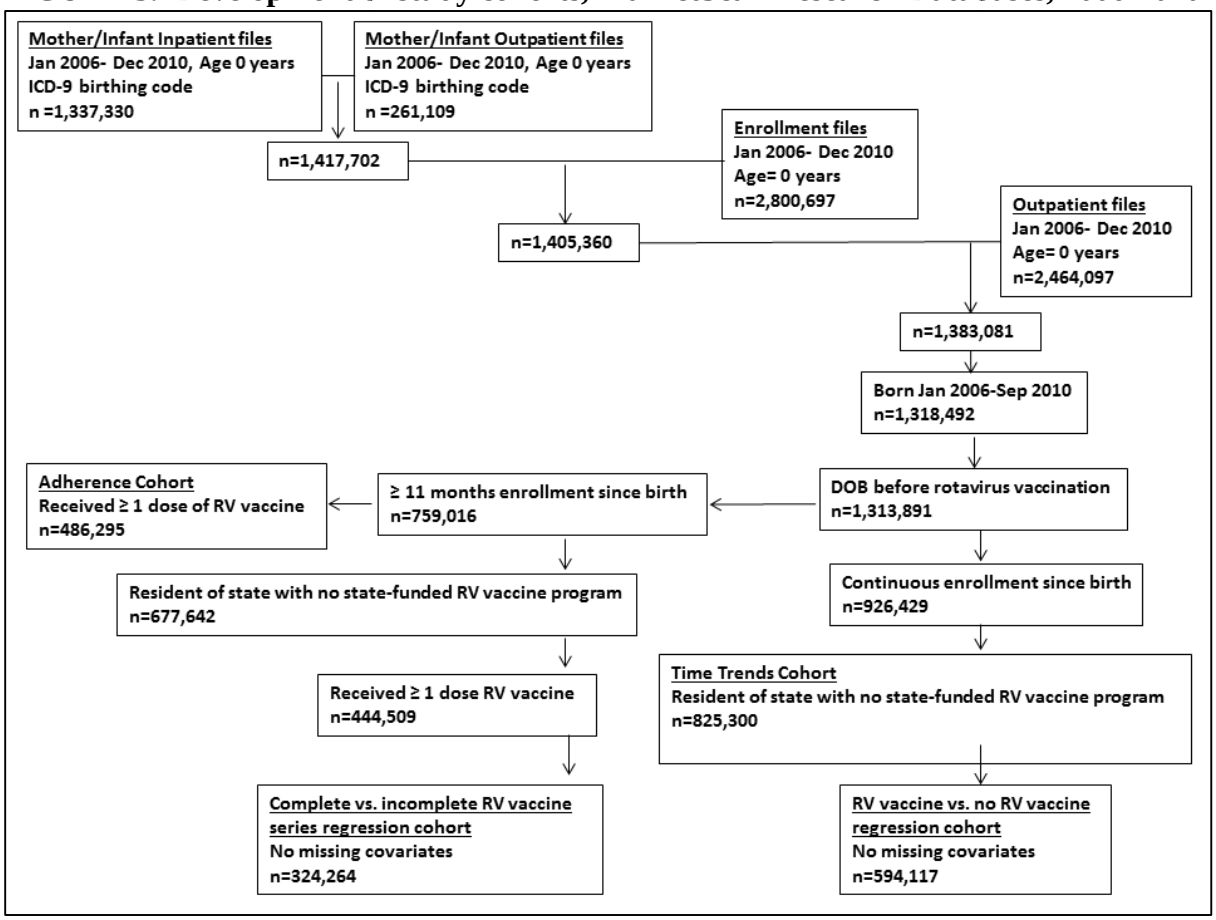
Variable	No. infants receiving ≥1 dose of RV5 or RV1 in category, born 2006-2010 (%)	Bivariate RR, born 2006-2010 (95% CI)	Multivariable RR, born 2006-2010 (95% CI)	Multivariable RR, born 2006 (95% CI)	Multivariable RR, born 2009 (95% CI)
Overall	259,701 (80.1)	---	---	---	---
Sex					
Female	127,460 (80.3)	Ref.	Ref.	Ref.	Ref.
Male	132,241 (79.9)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.98 (0.97-1.00)	1.00 (0.99-1.00)
DTaP vaccination					
No	2502 (62.6)	Ref.	Ref.	Ref.	Ref.
Yes	257,199 (80.3)	1.28 (1.25-1.31)	1.26 (1.23-1.29)	1.47 (1.32-1.63)	1.24 (1.19-1.29)
Hospitalized					
No 252,144 (80.2)	Ref.	Ref.	Ref.	Ref.	
Yes	7557 (77.3)	0.96 (0.95-0.98)	0.97 (0.96-0.99)	1.00 (0.96-1.04)	0.97 (0.95-0.98)
Number of siblings <10 years					
0	120,863 (82.2)	Ref.	Ref.	Ref.	Ref.
1	99,233 (79.5)	0.97 (0.96-0.97)	0.96 (0.96-0.97)	0.96 (0.95-0.98)	0.97 (0.96-0.98)
2	32,500 (76.3)	0.93 (0.92-0.93)	0.92 (0.92-0.93)	0.91 (0.89-0.93)	0.93 (0.92-0.94)
3 or more	7105 (72.4)	0.88 (0.87-0.89)	0.88 (0.87-0.89)	0.88 (0.84-0.92)	0.89 (0.87-0.91)
Mother's age (years)					
<25	21,999 (73.9)	0.91 (0.90-0.91)	0.91 (0.91-0.92)	0.91 (0.88-0.93)	0.93 (0.91-0.94)
25-<30	81,946 (79.6)	0.98 (0.97-0.98)	0.98 (0.98-0.98)	0.97 (0.95-0.99)	0.98 (0.98-0.99)
30-<35	97,386 (81.5)	Ref.	Ref.	Ref.	Ref.
35-40	48,715 (81.2)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.98-1.02)	1.00 (0.99-1.01)
≥40	9655 (80.1)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.97 (0.93-1.01)	0.98 (0.97-1.00)
Primary provider type					
Pediatrician	171,512 (82.0)	1.16 (1.14-1.17)	1.13 (1.11-1.14)	1.23 (1.16-1.31)	1.14 (1.12-1.16)
Family physician	8554 (70.9)	Ref.	Ref.	Ref.	Ref.
Other providers	48,874 (77.4)	1.09 (1.08-1.11)	1.07 (1.06-1.08)	1.17 (1.10-1.24)	1.09 (1.07-1.11)

No consistent provider type	30,761 (77.1)	1.09 (1.07-1.10)	1.07 (1.06-1.08)	1.18 (1.11-1.25)	1.08 (1.06-1.10)
Network of provider type					
In-network	234,753 (80.1)	1.01 (1.00-1.01)	1.00 (0.99-1.00)	1.00 (0.97-1.03)	0.97 (0.96-0.99)
Out of network or mix of networks	24,948 (79.9)	Ref.	Ref.	Ref.	Ref.
Health plan type					
Basic, comprehensive, or high deductible	3639 (81.0)	1.01 (1.00-1.03)	1.02 (1.00-1.03)	0.98 (0.91-1.04)	1.01 (0.99-1.03)
EPO or PPO	183,987 (79.8)	Ref.	Ref.	Ref.	Ref.
HMO	40,726 (80.9)	1.01 (1.01-1.02)	1.00 (1.00-1.01)	1.02 (1.00-1.04)	0.99 (0.98-1.00)
POS or POS with capitation	24,960 (80.2)	1.01 (1.00-1.01)	1.00 (1.00-1.01)	1.02 (1.00-1.05)	0.99 (0.98-1.01)
CDHP	6389 (81.2)	1.02 (1.01-1.03)	1.01 (1.00-1.02)	1.04 (0.99-1.08)	1.00 (0.99-1.02)
Region of residence					
Northeast	29,415 (80.7)	1.01 (1.01-1.02)	0.99 (0.99-1.00)	1.05 (1.02-1.08)	0.97 (0.96-0.98)
Midwest	78,228 (80.8)	1.01 (1.01-1.02)	1.02 (1.02-1.03)	1.01 (1.00-1.03)	1.03 (1.02-1.03)
South	131,635 (79.8)	Ref.	Ref.	Ref.	Ref.
West	20,423 (78.5)	0.98 (0.98-0.99)	0.99 (0.98-0.99)	0.93 (0.90-0.97)	0.99 (0.98-1.00)
Type of residence					
Metro with ≥1 M pop	160.617 (81.3)	Ref.	Ref.	Ref.	Ref.
Metro with 250,000 – 1 M pop	47,204 (81.1)	1.00 (0.99-1.00)	1.01 (1.00-1.01)	1.01 (0.99-1.03)	1.01 (1.00-1.02)
Metro with <250,000 pop	24,533 (77.7)	0.96 (0.95-0.96)	0.98 (0.97-0.98)	0.96 (0.94-0.99)	0.98 (0.97-0.99)
Urban with ≥20,000 pop, adjacent to metro area	8095 (76.1)	0.94 (0.93-0.95)	0.96 (0.95-0.97)	0.87 (0.83-0.92)	0.99 (0.97-1.01)
Urban with ≥20,000 pop, not adjacent to metro area	3869 (74.7)	0.92 (0.90-0.93)	0.94 (0.94-0.96)	0.91 (0.86-0.97)	0.95 (0.92-0.97)
Urban with 2500-19,999 pop, adjacent to metro area	9000 (73.5)	0.90 (0.89-0.91)	0.93 (0.92-0.94)	0.91 (0.87-0.95)	0.94 (0.92-0.95)
Urban with 2500-19,999 pop, not adjacent to metro area	3997 (70.0)	0.86 (0.85-0.88)	0.90 (0.88-0.91)	0.84 (0.78-0.90)	0.90 (0.87-0.92)
Rural or <2500 population, adjacent to metro area	1333 (77.3)	0.95 (0.93-0.97)	0.98 (0.95-1.0)	0.94 (0.84-1.04)	0.98 (0.94-1.03)
Rural or <2500 population,	1053 (71.7)	0.88 (0.85-0.91)	0.92 (0.89-0.95)	1.03 (0.92-1.15)	0.92 (0.87-0.98)

not adjacent to metro area

Abbreviations: CDHP, Consumer Directed Health Plan; DTaP, diphtheria, tetanus, and acellular pertussis; EPO, Exclusive Provider Organization; HMO, Health Maintenance Organization; Metro, metropolitan; Pop, population; POS, Point of Service; PPO, Preferred Provider Organization; RV1, monovalent rotavirus vaccine; RV5, pentavalent rotavirus vaccine

FIGURE 3. Development of study cohorts, MarketScan Research Databases, 2006-2010



B. Direct, indirect, total and overall effectiveness of the rotavirus vaccines in preventing gastroenteritis hospitalizations in privately-insured US children, 2007-2010

1. Introduction

Most Phase III vaccine efficacy trials focus on determining the direct effectiveness of vaccination, generally measured as one minus the relative risk in the vaccinated group compared to the unvaccinated group. Some clinical trials and many post-licensure studies also measure herd protection or indirect vaccine effectiveness (VE), defined as population-level effects of widespread vaccination on people not receiving the vaccine.(1) Two additional measures of VE, total and overall VE, account for both the direct and indirect effectiveness of a vaccine (Figure 4). Total VE combines the direct and indirect VE on individuals receiving the vaccine, while the overall VE weights the average of the total VE on individuals receiving the vaccine with the indirect VE on individuals not receiving the vaccine.(1) Total VE can thus be interpreted as the complete benefit of vaccination in vaccine recipients and overall VE can be interpreted as the public health benefit of vaccination. Despite challenges in estimating the four types of VE, they are essential to understand the real-world impact of a vaccine.(16-18)

We compared direct, indirect, total and overall rotavirus VE estimates in preventing rotavirus gastroenteritis (RGE) and acute gastroenteritis (AGE) hospitalizations from 2007 to 2010 in a commercially insured population of US infants and children 8 to 20 months of age. We also examined how the absolute number of gastroenteritis hospitalizations varied as effectiveness estimates varied through the years. We hypothesized that the direct VE estimates would remain stable

over time, but the indirect, total, and overall VE estimates which are or include measures of herd protection would increase as the percentage of rotavirus-vaccinated children increased over time. Furthermore, failing to account for herd protection, even among the vaccinated, would underestimate the absolute number of hospitalizations prevented by the vaccines. Briefly, the pentavalent rotavirus vaccine (RV5), RotaTeq (Merck & Co., Inc.), administered orally in three doses at ages two, four, and six months, has been recommended for routine use among US infants since February 2006 and the monovalent rotavirus vaccine (RV1), Rotarix (GlaxoSmithKline Biologicals), administered orally in two doses at ages two and four months, has been recommended since June 2008 by the Advisory Committee on Immunization Practices (ACIP).(19, 20)

2. Methods

Data Source. The MarketScan Research Databases contain data from a large number of individuals in the US with commercial insurance. In 2010, the database included approximately 920,000 infants.

Design and Population. Infants with continuous enrollment during infancy, at least one outpatient record, and an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) birthing code (V30-V39) between May 1, 2000 and April 30, 2005 or May 1, 2006 and April 30, 2010 were abstracted from the databases. Birthing codes identified in mothers' claims were also used to identify birth dates of potentially eligible infants. If an infant or mother had a V30-V39 claim coded on multiple dates, the date of the first V30-V39 code was used as the birth date. Since follow-up for RGE began when infants turned eight months and

continued until a maximum age of 20 months, infants receiving doses of rotavirus vaccine after age eight months were excluded so that rotavirus vaccine status could be treated as a time-independent variable.

Infants with commercial insurance failing to receive vaccines with high coverage rates (≥95%) may have differed from infants receiving such vaccines with respect to unmeasured confounding factors, so we required all infants in our study to be vaccinated with at least one dose of diphtheria, tetanus, and acellular pertussis vaccine (DTaP), using the following Current Procedural Terminology (CPT) codes: 90696, 90698, 90700, 90701, 90702, 90714, 90715, 90718, 90720, 90721, and 90723.

Outcome, Exposure, and Covariate Measurements. Outcomes of RGE were identified using ICD-9-CM codes. Any of the 15 coding fields in the inpatient files of the databases was used to capture the ICD-9-CM code for rotavirus-specific disease, 008.61. Since rotavirus-coded events underestimate the true burden of rotavirus disease due to lack of routine laboratory testing and coding, we performed sensitivity analyses, assuming 25% and 50% sensitivity of the 008.61 code, and also abstracted and examined outcomes related to the following acute gastroenteritis (AGE) ICD-9-CM codes: bacterial (001-005, excluding 003.2, and also including 008.0-008.5), parasitic (006-007, excluding 006.3-006.6), and viral diarrhea (008.6 and 008.8); diarrhea of undetermined etiology (presumed infectious [009.0-009.3] and presumed noninfectious [558.9]); and diarrhea not otherwise specified (787.91).(21-25)

RV5 and RV1 vaccination status were identified using the CPT codes, 90680 and 90681, and treated as time-independent. To increase the specificity of vaccination status, we excluded infants living in states with state-funded rotavirus

vaccine programs (Alaska, Idaho, Massachusetts, Maine, North Dakota, New Hampshire, New Mexico, Oregon, Rhode Island, Vermont, Washington, Wisconsin, and Wyoming).(25, 26)

To help account for different levels of exposure to rotavirus due to household and geographic variations in rotavirus vaccine coverage, disease, and mixing behaviors, we examined the number of other dependents less than 10 years old covered by the same insurance holder as the infant (considered "older siblings"), and also the region and rurality of the child's residence, as defined by the US Department of Agriculture (USDA), Economic Research Service.(27) To characterize general infant health and potential differences in susceptibility to rotavirus disease, we compared the percentage of infants less than two months that had overnight hospital stays unrelated to AGE prior to age two months.

Data Analysis. We used Cox proportional hazard regression models to calculate hazard rate ratios, comparing the hazard of RGE or AGE hospitalization among vaccinated infants to unvaccinated infants entering the cohort in 2007, 2008, 2009, or 2010 and subtracting the result from one to obtain direct VE estimates by calendar year. We similarly calculated the indirect, total, and overall VE, varying the comparison cohorts as appropriate. For indirect VE, we compared unvaccinated infants followed during each calendar year of the rotavirus vaccine period, 2007-2010, to (unvaccinated) infants followed during the baseline period, 2001-2005. For total VE, we compared vaccinated infants followed during each calendar year of the rotavirus vaccine period to (unvaccinated) infants followed during the baseline period. For overall or average VE, we compared all vaccinated and unvaccinated

infants during each calendar year of the rotavirus vaccine period to (unvaccinated) infants followed during the baseline period.

In all regression analyses, age served as the underlying time variable, and infants were censored when they experienced a RGE or AGE hospitalization, lost continuous enrollment, reached their 20 month birthday, or reached the end of the study period on December 31, 2010, whichever occurred first. Results were stratified by year to account for increasing vaccination coverage and adjusted for month of birth to account for the seasonality of rotavirus. Infants and children were allowed to contribute person-time during two calendar years. For example, an infant turning eight months old on October 1, 2007, would contribute three person-months in 2007, and then re-enter the cohort on January 1, 2008 at age 11 months and contribute up to nine more calendar months of person-time in 2008.

Incidence rate differences based on the case count and person-years in our population, and additional analyses assuming 25% and 50% sensitivity and 100% specificity of the RGE and AGE ICD-9-CM codes were calculated to determine the absolute number of RGE and AGE hospitalizations prevented by the rotavirus vaccine program in our cohort.

All analyses were conducted in SAS, version, 9.2 (SAS Institute, Inc). This study was exempt from human subjects review by the Institutional Review Board at the University of North Carolina since only deidentified data were used.

3. Results

Cohort. Approximately half (52%) of the 3.94 million infants identified in the enrollment files between January 2000 and December 2010 had an ICD-9 birthing

code (V30-39) with a date of service in the infant or mothers' inpatient or outpatient claims (Figure 5). After additional exclusions, among the 905,718 children in our final cohort, 627,818 (78%) were born during the rotavirus vaccination period, May 2006-April 2010 (476,576 were vaccinated with a rotavirus vaccine, 151,242 were unvaccinated) and followed during 2007, 2008, 2009, and/or 2010. The other 277,900 children were born during the pre-vaccine period, May 2000-April 2005, and followed in 2001, 2002, 2003, 2004, and/or 2005. Among all 627,818 children followed during the rotavirus vaccine period, 379,262 (60%) were followed during parts of two calendar years.

Characteristics of cohort. Almost 76% of the children born during the rotavirus vaccine period received at least one dose of RV5 or RV1 of which 79% completed the series. Vaccination rates varied by calendar year, ranging from 51% in 2007 to 86% in 2010 (Table 4). Most (91%) vaccinated children received RV5, and over 3% received doses of RV5 and RV1.

Nearly 4% of children were hospitalized overnight for a non-AGE diagnosis by age two months, and this percentage was slightly lower among the rotavirus-vaccinated compared to the unvaccinated in 2009 and 2010. The mean number of older siblings in each household was slightly lower in households with rotavirus-vaccinated compared to unvaccinated children, but was stable across calendar years. Children residing in the Northeast, North-Central, and Western US had lower rates of rotavirus vaccination than children residing in the Southern US; children residing in the South also composed almost half of the entire study population. Children residing in the Western US were better represented during the baseline years than in the

vaccine years (19% versus 11%). In each calendar year, most children (86-89%) resided in metropolitan areas, with 66-69% of them residing in metropolitan areas with populations of one million persons or more. There was a slight increase in the number of children residing in large metropolitan areas with each successive calendar year. Children residing in metropolitan areas were 3 to 5% more likely than those residing in non-metropolitan areas to be vaccinated across each calendar year.

RGE hospitalizations. Twenty-three of 905,718 infants were dropped from the cohort because their cohort entry date (8 month birthday) equaled their cohort exit date (RGE hospitalization date, (n=4) or loss of health plan enrollment date, (n=19)). Among the 905,695 remaining children, 1016 (0.11%) were hospitalized for RGE during follow-up. The percentage of infants and children hospitalized for RGE decreased during each calendar year or period as follows: 2001-2005, 722/277,899 (0.26%); 2007, 63/133,309 (0.05 %); 2008, 114/266,941 (0.04%); 2009, 96/311,253 (0.03%); 2010, 21/296,323 (0.01%). The incidence rate of RGE hospitalization in March, the traditional peak of rotavirus activity, ranged from 121 per 10,000 child-years during the pre-vaccine period to 1 per 10,000 child-years in 2010 (Figure6). The pattern of RGE hospitalization rates closely followed the pattern of rotavirus activity in reports published elsewhere (28-31).

AGE hospitalizations. Of the 905,678 infants whose cohort entry date did not equal their cohort exit date with regards to AGE hospitalizations, 4483 (0.49%) had an AGE diagnosis. The percentage of infants and children hospitalized for AGE during the pre-vaccine years was 0.73% (2021/277,893). This percentage declined to 0.31% (413/133,306) in 2007 and continued to decline steadily during the vaccine

years, reaching 0.17% (507/296,120) in 2010. Overall, nearly one-quarter of the AGE diagnoses were coded as RGE. However, the proportion of children with AGE diagnostic codes that corresponded to RGE generally decreased with each successive calendar year or period (2001-2005, 36% (722/2021); 2007, 15% (63/413); 2008, 16% (114/730); 2009, 12% (96/812); 2010, 4% (21/507)). Despite the decline in the proportion of AGE diagnoses coded as RGE through the years, the monthly incidence rate of AGE by year followed a similar pattern as the monthly incidence rate of RGE by year (Figure 7).

Rotavirus VE. Direct VE of one or more doses of RV5 or RV1 in preventing RGE hospitalizations between ages 8 and 20 months ranged from 87 to 92% (Table 5, Figure 8). The indirect VE varied more widely, from 14% (95% CI, -14-36%) in 2007 to 82% (95% CI, 70-90%) in 2010 (Figure 9) . Accounting for both direct and indirect VE among the rotavirus-vaccinated infants yielded a total VE estimate that increased from 91% (95% CI, 73-97%) in 2007 to 98% (95% CI, 96-99%) in 2010. The overall VE ranged from 40% (95% CI, 20-54%) in 2007 to 96% (93-97%) in 2010 (Figure 10). The overall VE estimates were low in 2007 compared to 2008-2010, but the direct and total VE estimates were high (≥87%) across all four calendar years. The rotavirus VE estimates were substantially lower in the prevention of AGE hospitalization, but generally followed a similar pattern as the VE estimates in the prevention of RGE hospitalization. Notable exceptions included the direct VE estimates which increased through 2009 and then decreased in 2010, and the total VE estimates which increased four-fold from 2007 to 2008 (Table 6, Figures 8-10).

Absolute effects of rotavirus vaccination. Under the assumption of perfect sensitivity and specificity of the RGE ICD-9-CM code, 31 to 33 RGE hospitalizations per 10,000 child-years were prevented in vaccinated children and 10 to 26 RGE hospitalizations per 10,000 child-years were prevented in unvaccinated children in our cohort during each calendar year, 2007- 2010 (among vaccinated infants, 6 to 21 hospitalizations were prevented as a result of direct effects, while 10 to 26 hospitalizations were prevented from indirect effects) (Table 7). Irrespective of vaccination status and thus from a public health viewpoint, in order to prevent one RGE hospitalization in our cohort, 315 to 421 children required a rotavirus vaccination. Assuming a more realistic scenario of 50% and 25% sensitivity of the RGE ICD-9 code, only 80 to 210 children may have required a rotavirus vaccination in order to prevent one RGE hospitalization. Compared to estimates relying only on RGE diagnostic codes, using AGE diagnostic codes to estimate the number of RGE hospitalizations prevented in our cohort increased the number by 130-180% among rotavirus-vaccinated children each calendar year (Table 8).

4. Discussion

Receiving one or more doses of RV5 or RV1 was highly effective in preventing RGE hospitalizations in this population of commercially-insured US infants and children aged 8 to 20 months. Direct VE was high across each calendar year, ranging from 87% in 2007 and 2008 to 92% in 2009, and indirect protection increased the VE among the rotavirus-vaccinated by an additional 3 to 8% each calendar year. By comparison, in clinical trials, a complete series (three doses) of RV5 was 98% (95% CI, 88-100%) effective against severe RGE for the first full

rotavirus season post-vaccination, and a complete series (two doses) of RV1 was 85% (95% CI, 70-94%) effective against hospitalizations for severe RGE from two weeks after the second dose until one year of age.(32, 33) Interestingly, our direct VE estimates were similar to the estimates calculated in the aforementioned clinical trials, despite the fact that 21% of the infants in our post-marketing study did not complete a rotavirus vaccine series. In our view, this observation has two possible explanations. First, partial completion of a rotavirus vaccine series may still result in high direct VE. This observation has been supported by other post-marketing studies, including an active, prospective population-based case-control study of laboratory-confirmed RGE hospitalizations and emergency department visits in three US counties from January-June 2006-2009 where the direct VE of RV5 for one, two, and three dose rotavirus vaccine regimens was 74% (95% CI, 37-90%), 88% (95% CI, 66-96%), and 87% (95% CI, 71-94%) in children <4 years of age, and another study that used a database from a large US health insurer to estimate one and two dose direct VE estimates in preventing RGE hospitalizations and emergency department visits for RV5 during the 2007 and 2008 rotavirus seasons (one-dose VE=88%, 95% CI,45-99% and two-dose VE=94%, 95% CI,61-100%).(34, 35) The alternative explanation may be that our direct VE estimates are biased upward. A mathematical model showed that when a vaccine provides indirect protection and the percent vaccinated in subpopulations is not equal (the likely scenario for most post-marketing studies), then direct VE estimates may be biased upward from clinical trial efficacy estimates because the vaccinated sub-population will receive more indirect protection than the unvaccinated sub-population, assuming that there are no other differences between

the vaccinated and unvaccinated groups.(36) In our study, this bias would have increased during the later years when the percentage of rotavirus-vaccinated children was highest which could explain why the direct VE estimates in our cohort in 2009 and 2010 were 5 and 3% higher than in 2007 and 2008. Thus, it is important to realize that our direct VE estimates may in fact have included indirect benefits, and that the importance of indirect benefits in rotavirus-vaccinated children may have been further underscored in the total VE estimate since the direct VE was already high and VE cannot exceed 100%. Supporting the importance of indirect protection among rotavirus-vaccinated children was our result which showed that the direct VE estimates underestimated the total number of RGE hospitalizations prevented by 1.5 to 5.3-fold even though the direct VE estimate was only 3 to 8% lower than the total VE estimate.

We expected indirect or herd protection against RGE hospitalizations to increase with each successive calendar year from 2007 to 2010, but this was not the case. The calendar year 2009 had a slightly lower indirect VE estimate than 2008 (44% versus 40%). Although a lack of difference between these indirect VE estimates cannot be ruled out since their confidence intervals overlap, the apparent decline of indirect VE in 2009 is worth further consideration. Not only a decline, but a total absence of indirect protection from the rotavirus vaccine during the 2009 rotavirus season has been observed in other studies.(25, 37, 38), and it has been hypothesized that the low levels of rotavirus activity during the 2008 season allowed unvaccinated children to pass through the season without exposure to wild-type virus until 2009.(37) However, since rotavirus activity in the US was also curtailed in 2009

and the indirect VE estimate more than doubled to 82% in 2010, additional explanations may be needed.(39) A study modeling direct and indirect transmission dynamics of rotavirus vaccination in England and Wales found that assuming 90% rotavirus vaccination coverage, indirect effects would reduce RGE 1.8-2.9 times more than expected from direct effects during the first year after initiation of a vaccination program, but that over a 5-year period, the indirect benefits would decline.(40) Additional years of follow-up and other data sources may be needed to better establish time trends related to the indirect effectiveness of rotavirus vaccination in the US. Nonetheless, due to the demonstrated importance of indirect VE among both vaccinated and unvaccinated children, we recommend that the indirect effectiveness of vaccines be measured prior to the post-market phase when possible. This is especially important for candidate vaccines with limited direct VE, but potentially strong indirect VE (e.g., cholera vaccines, rotavirus vaccines in certain developing countries).(41, 42)

Our study has two important strengths. First, across both time and vaccination status, the five calendar years or periods we examined were generally well balanced on selected covariates which included proxies for health, potential sources of rotavirus infections, and population-level rotavirus vaccination coverage and mixing patterns. Since all cohort members were commercially insured and required to have at least one outpatient record during infancy as well as at least one dose of DTaP, such standards may have led to the relatively good balance between the groups with regards to the measured, and hopefully, unmeasured potential confounders. Second, since we used Cox proportional hazards regression, our analyses inherently adjusted

for age and we also stratified by year to account for increasing vaccination coverage and adjusted for month of birth to account for the changing seasonality of rotavirus over the study period. Further adjustment using the covariates we described in Table 1 did not appreciably change our VE estimates so they were not presented. This lack of change was not surprising since our groups seemed reasonably well balanced.

Our results should be interpreted with some caution due to four possible limitations. First, the RGE ICD-9-CM code likely had low sensitivity which would bias the number of RGE hospitalizations prevented downward. Thus, we conducted sensitivity analyses on the number of RGE hospitalizations prevented assuming 25% and 50% sensitivity of the RGE ICD-9-CM code.(21, 43) These analyses made assumptions that may not have been entirely realistic, including that the sensitivity did not vary over time or between vaccinated and unvaccinated children and that estimates of 25 and 50% sensitivity and 100% specificity were reasonable. AGE ICD-9-CM diagnostic codes were also subject to low sensitivity. A recent study conducted at three US children's hospitals found that only 52% of children hospitalized with AGE received a qualifying diagnostic code at discharge.(44) Fortunately, low sensitivity of RGE or AGE ICD-9-CM codes would not bias VE estimates if specificity was high which was assumed based on research as well as other studies showing similar RGE and AGE hospitalization patterns as our study. (21,23, 29-31) Second, we limited the age range of follow-up to infants and children 8 to 20 months. Some studies suggest that the US rotavirus vaccination program may have increased the mean age at which infants and children are first infected with rotavirus, and thus potentially hospitalized with RGE.(45, 46) If the shift in mean age

has been dramatic, the rotavirus vaccines in the later years (e.g., 2010) may appear more effective overall than in the earlier years simply because the burden of RGE hospitalization has shifted to older age groups. A US strain surveillance study of 919 EIA-confirmed RGE cases found that while the mean age of cases was 13.1 and 13.3 months during the 2005-2006 and 2006-2007 rotavirus seasons, the mean age of cases increased to 17.7 months during the 2007-2008 rotavirus season.(46) Despite this potential shift, our study would still accurately document rotavirus VE among 8 to 20 month olds, and since RGE hospitalizations are generally considered most serious in very young children (e.g., <2 years), our study would still have captured many of the most clinically significant cases. Third, our study considered infants receiving any number of doses of rotavirus vaccine as "vaccinated" and did not compare the direct VE of RV5 to RV1 due to the limited number of infants vaccinated with RV1. A few comparative effectiveness studies as well as studies assessing partial rotavirus vaccine effectiveness have been published, and ongoing monitoring should continue to assess these questions.(35, 41, 47-50) Finally, our study may have limited generalizability since it involved only US infants and children with commercial insurance, and did not include those with Medicaid insurance or the uninsured population. However, our study is one of the largest rotavirus VE studies to-date, and assesses effectiveness in the population of infants and children most likely to receive the rotavirus vaccines in the US.

If a vaccine has high direct VE, such measurements may only slightly underestimate the total VE which also account for indirect protection among vaccinated persons. However, failing to account for indirect VE may severely

underestimate the impact of important public health outcomes, such as the absolute number of RGE hospitalizations prevented among vaccinated children in our cohort. For this reason, VE studies should strive to provide both direct and indirect VE estimates, and also report results in the context of absolute benefits.

5. Figures and Tables

FIGURE 4. Types of Vaccine Effectiveness as Described by Halloran et al (1)

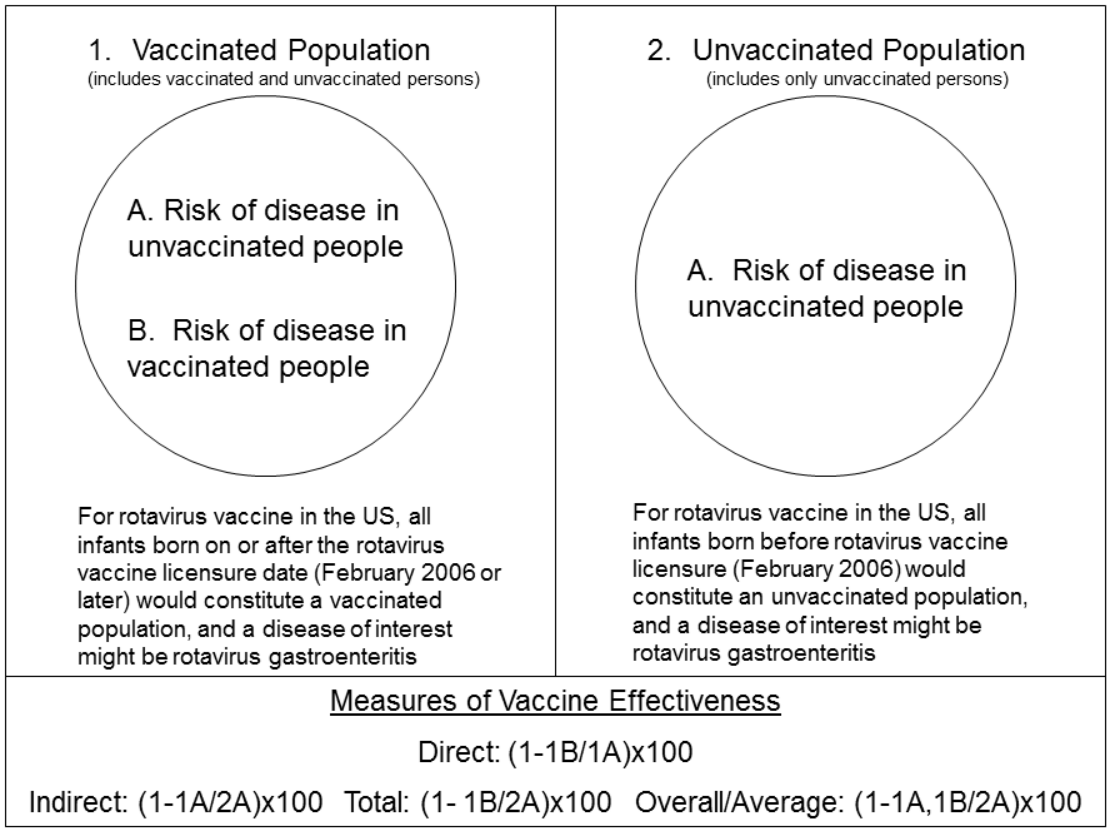
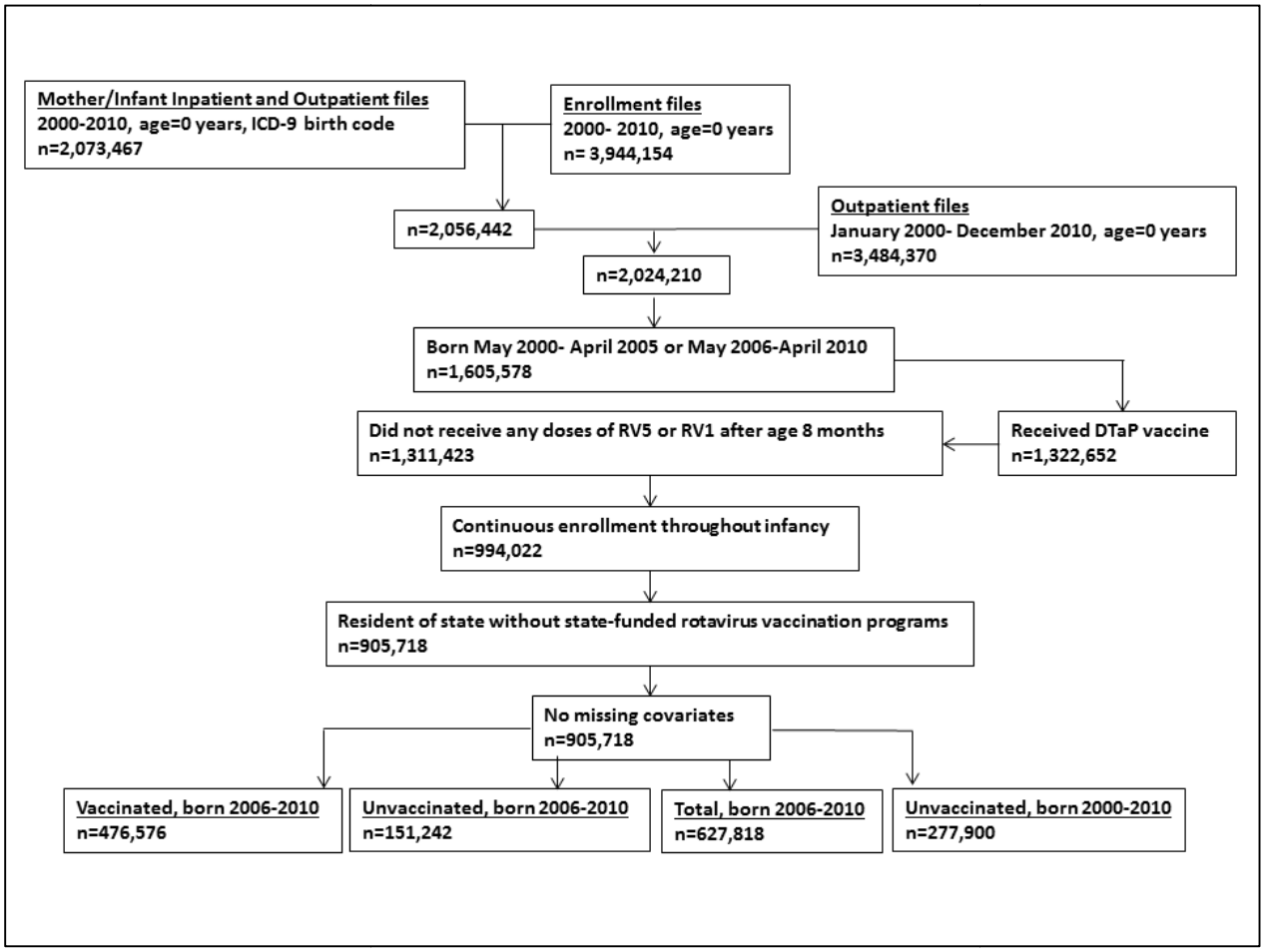


FIGURE 5. Cohort Study Design for Rotavirus Vaccine Effectiveness Study in a Population of Commercially Insured Infants and Children 8 to 20 Months, 2007-2010



Abbreviations: DTaP, diphtheria, tetanus, and acellular pertussis vaccine; ICD-9, International Classification of Diseases, 9th Revision; RV1, monovalent rotavirus vaccine; RV5, pentavalent rotavirus vaccine

TABLE 4. Characteristics of Commercially Insured US Infants and Children Vaccinated or Unvaccinated with RV5 or RV1, 2001-2010 (n=905,718)

	2007*		2008*		2009*		2010*		2001-2005
Variable	V	Not V	V	Not V	V	Not V	V	Not V	
Overall	68,380	64,932	175,768	90,883	249,840	61,136	254,249	41,892	277,900 (100)
	(51.29)	(48.71)	(65.92)	(34.08)	(80.34)	(19.66)	(85.85)	(14.15)	
Male	34,807	33,380	89,376	46,719	127,673	31,521	130,331	21,768	143,275
	(51.05)	(48.95)	(65.67)	(34.33)	(80.20)	(19.80)	(85.69)	(14.31)	
Hospitalized overnight for non-AGE, <2 months	2,744	2,563	6,856	3,647	8,995	2,459	8793	1689	10,849
	(51.71)	(48.29)	(65.28)	(34.72)	(78.53)	(21.47)	(83.89)	(16.11)	
Mean number of siblings (std)	0.81	0.88	0.81	0.90	0.80	0.93	0.76	0.91	0.85
	(0.97)	(1.02)	(0.98)	(1.04)	(0.98)	(1.09)	(0.96)	(1.09)	(1.04)
Region of residence									
Northeast	4,692	6,119	14,799	9,869	28,395	10,183	35,312	9203	28,956
	(43.40)	(56.60)	(59.99)	(40.01)	(73.60)	(26.40)	(79.33)	(20.67)	
North-Central	21,296	22,473	52,672	31,299	70,875	18,988	70,936	11,211	67,895
	(48.66)	(51.34)	(62.73)	(37.27)	(78.87)	(21.13)	(86.35)	(13.65)	
South	36,568	28,488	91,886	38,050	125,634	24,003	117,518	15,593	127,956
	(56.21)	(43.79)	(70.72)	(29.28)	(83.96)	(16.04)	(88.29)	(11.71)	
West	5,824	7,852	16,411	11,665	24,936	7,962	30,483	5885	53,093
	(42.59)	(57.41)	(58.45)	(41.55)	(75.80)	(24.20)	(83.82)	(16.18)	
Population density of residence									
Metro with ≥1 million population	38,636	38,108	102,075	52,069	150, 601	35,456	156,027	25,046	160,282
	(50.34)	(49.66)	(66.22)	(33.78)	(80.94)	(19.06)	(86.17)	(13.83)	
Metro with 250,000 – 1 million population	13,173	10, 789	33,515	15,231	45,440	9,650	47,219	6777	54,512
	(54.97)	(45.03)	(68.75)	(31.25)	(82.48)	(17.52)	(87.45)	(12.55)	
Metro with <250,000 population	8,095	6,199	18,443	8,890	24,680	5,796	23,780	3769	27,543
	(56.63)	(43.37)	(67.48)	(32.52)	(80.98)	(19.02)	(86.32)	(13.68)	
Urban with ≥20,000 population, adjacent to metro area	2,613	2,673	6,375	3,749	8,376	2,535	8274	1689	10,412
	(49.43)	(50.57)	(62.97)	(37.03)	(76.77)	(23.23)	(83.05)	(16.95)	
Urban with ≥20,000 population, not adjacent to metro area	1,197	1,618	3,165	2,354	4,120	1,471	3722	889	5225
	(42.52)	(57.48)	(57.35)	(42.65)	(73.69)	(26.31)	(80.72)	(19.28)	

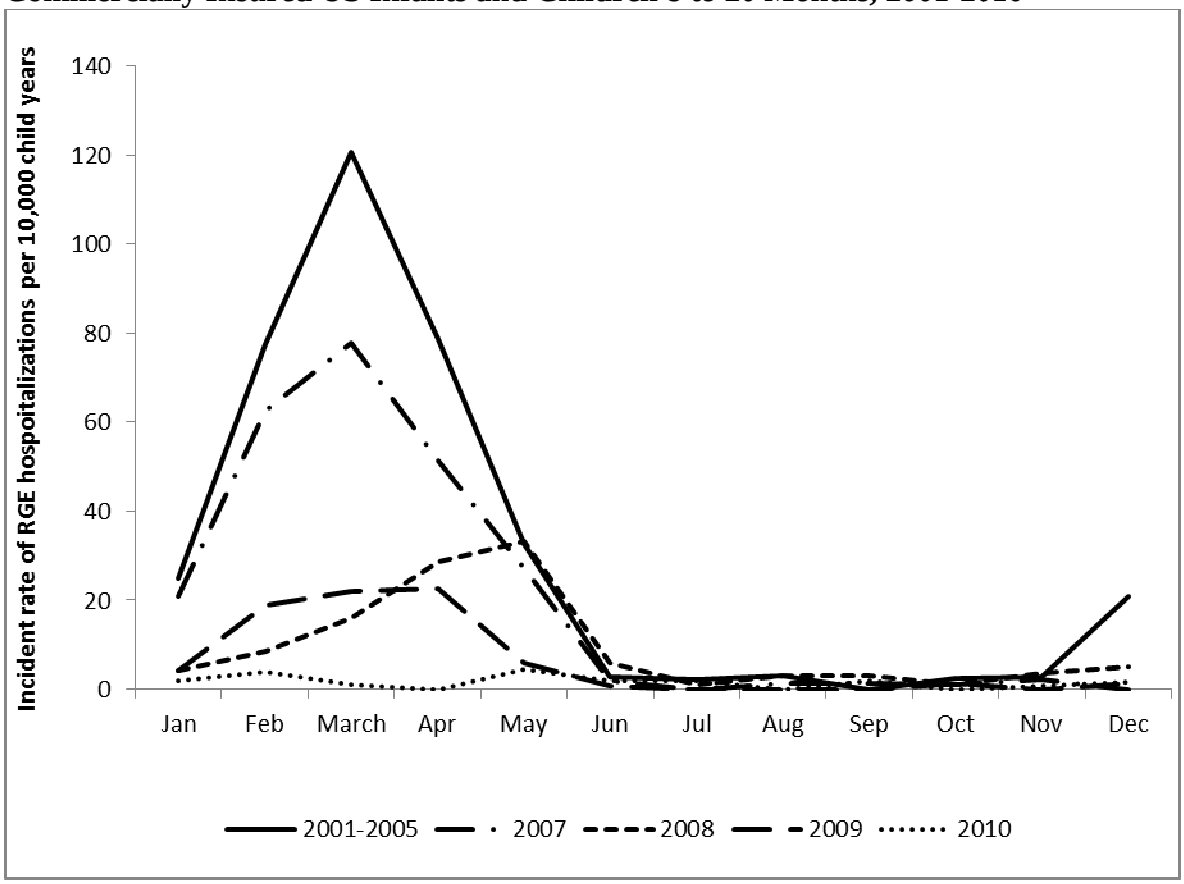
Urban with 2500-19,999 population, adjacent to metro area	2,744 (46.44)	3,165 (53.56)	7,147 (59.75)	4,814 (40.25)	9,641 (74.49)	3,302 (25.51)	9055 (81.42)	2067 (18.58)	11,909
Urban with 2500-19,999 population, not adjacent to metro area	1,266 (42.09)	1,687 (57.91)	3,263 (54.68)	2,704 (45.32)	4,530 (68.22)	2,110 (31.78)	3981 (76.47)	1225 (23.53)	4981
Rural or <2500 population, adjacent to metro area	394 (52.12)	362 (47.88)	951 (64.74)	518 (35.26)	1,351 (78.27)	375 (21.73)	1258 (87.42)	181 (12.58)	1673
Rural or <2500 population, not adjacent to metro area	302 (47.71)	331 (52.29)	834 (60.09)	554 (39.91)	1,101 (71.40)	441 (28.60)	933 (78.93)	249 (21.07)	1363

Abbreviations: AGE, acute gastroenteritis; IQR, interquartile range; Metro, metropolitan; RV1, monovalent rotavirus vaccine; RV5,pentavalent rotavirus vaccine; Std, standard deviation; V, vaccinated

*379,262 (60%) of infants and children were counted during two consecutive calendar years during the vaccine period, 2007-2010.

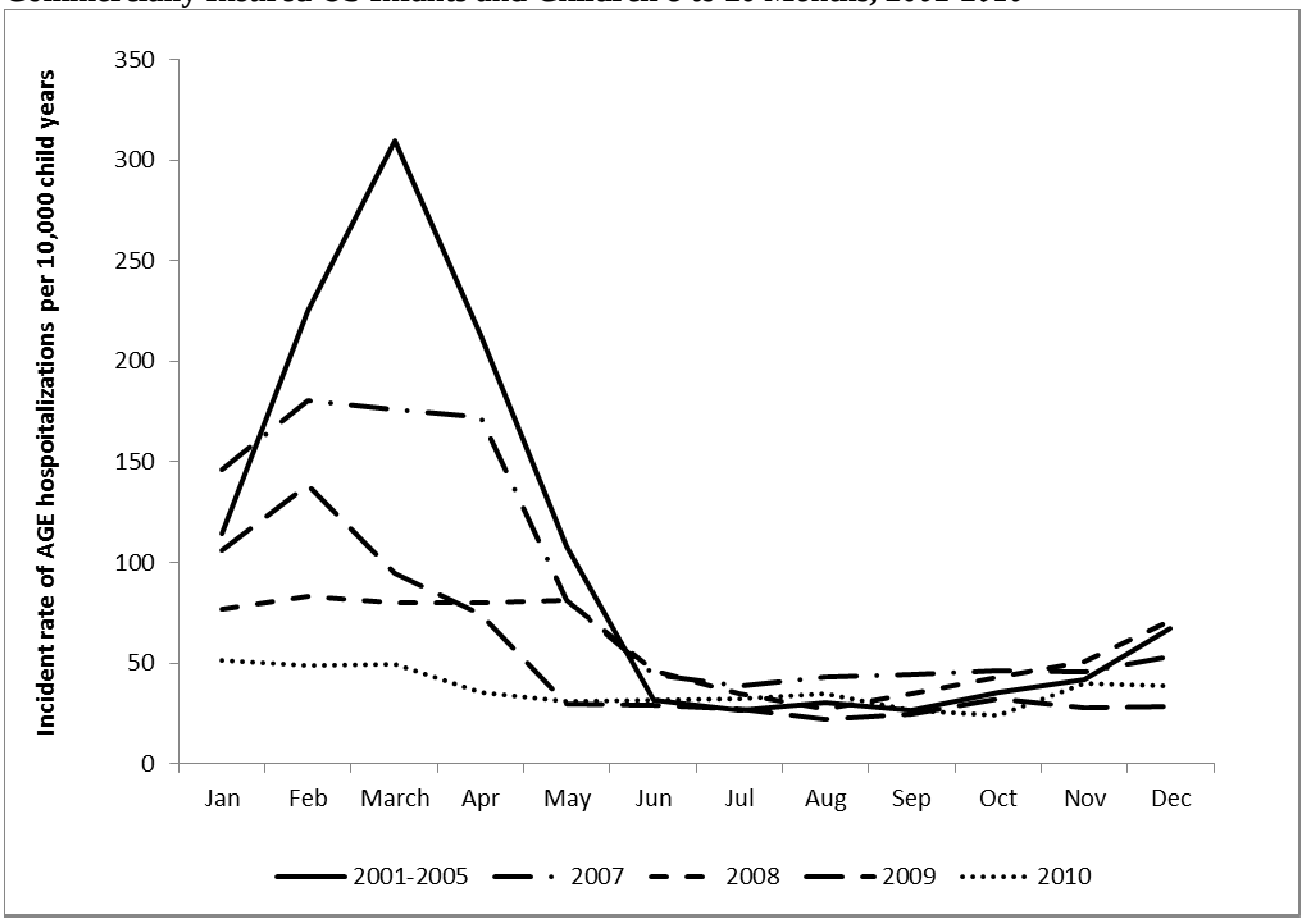
AGE as opposed to RGE cohort used for counts.

FIGURE 6. Incidence of RGE Hospitalizations per 10,000 Child-years Among Commercially Insured US Infants and Children 8 to 20 Months, 2001-2010



Abbreviations: RGE, rotavirus gastroenteritis

FIGURE 7. Incidence of AGE Hospitalizations per 10,000 Child-years Among Commercially Insured US Infants and Children 8 to 20 Months, 2001-2010



Abbreviations: AGE, acute gastroenteritis

TABLE 5. Rotavirus vaccine effectiveness estimates against RGE hospitalization in US Commercially Insured Infants and Children 8 to 20 Months, 2007-2010

		Direct effectiveness		Indirect effectiveness		Total effectiveness		Overall effectiveness	
Calendar Year	Percent vaccinated with ≥1 dose of RV5 or RV1	Unadjusted VE (95% CI)	Number of events/people in numerator Number of events/people denominator	Unadjusted VE (95% CI)	Number of events/people in numerator Number of events/people denominator	Unadjusted VE (95% CI)	Number of events/people in numerator Number of events/people denominator	Unadjusted VE (95% CI)	Number of events/people in numerator Number of events/people denominator
2007	51.3	87 58, 96	3/68,380 60/64,929	14 -14, 36	60/64,929 722/277,899	91 73, 97	3/68,380 722/277,899	40 20, 54	63/133,309 722/277,899
2008	65.9	87 80, 92	23/175,890 91/91,051	44 30, 55	91/91,051 722/277,899	92 88, 95	23/175,890 722/277,899	75 69, 79	114/266,941 722/277,899
2009	80.3	92 87, 95	22/250,035 74/61,218	40 24, 53	74/61,218 722/277,899	95 92, 97	22/250,035 722/277,899	83 79, 86	96/311,253 722/277,899
2010	85.9	90 75, 96	8/254,377 13/41,946	82 70, 90	13/41,946 722/277,899	98 96, 99	8/254,377 722/277,899	96 93, 97	21/296,323 722/277,899

Abbreviations: CI, confidence interval; RGE, rotavirus gastroenteritis; RV1, monovalent rotavirus vaccine; RV5, pentavalent rotavirus vaccine; VE, vaccine effectiveness

TABLE 6. Rotavirus vaccine effectiveness estimates against AGE hospitalization in US Commercially Insured Infants and Children 8 to 20 Months, 2007-2010

		Direct effectiveness		Indirect effectiveness		Total effectiveness		Overall effectiveness	
Calendar Year	Percent vaccinated with ≥1 dose of RV5 or RV1	Unadjusted VE (95% CI)	Number of events/people in numerator Number of events/people denominator	Unadjusted VE (95% CI)	Number of events/people in numerator Number of events/people denominator	Unadjusted VE (95% CI)	Number of events/people in numerator Number of events/people denominator	Unadjusted VE (95% CI)	Number of events/people in numerator Number of events/people denominator
2007	51.3	22 3, 37	142/68,378 271/64,928	-8 -24, 6	271/64,928 2021/277,893	12 -5, 27	142/68,378 2021/277,893	0 -13, 11	413/133,306 2021/277,893
2008	65.9	40 30, 48	413/175,765 317/90,882	24 15, 33	317/90,882 2021/277,893	48 43, 53	413/175,765 2021/277,893	40 35, 45	730/266,647 2021/277,893
2009	80.3	56 49, 62	512/249,838 300/61,136	9 -3, 19	300/61,136 2021/277,893	59 54, 62	512/249,838 2021/277,893	48 44, 52	812/310,974 2021/277,893
2010	85.9	41 27, 53	398/254,232 109/41,888	45 33, 54	109/41,888 2021/277,893	65 62, 69	398/254,232 2021/277,893	62 58, 66	507/296,120 2021/277,893

Abbreviations: AGE, acute gastroenteritis; CI, confidence interval; RV1, monovalent rotavirus vaccine; RV5, pentavalent rotavirus vaccine; VE, vaccine effectiveness

TABLE 7. Absolute Numbers of RGE Hospitalizations Prevented by the Rotavirus Vaccination Program in Commercially Insured US Infants and Children 8 to 20 Months, 2007-2010

Calendar year	Observed number of RGE hospitalizations in numerator	Number of person-years in numerator	Observed number of RGE hospitalizations in denominator	Number of person-years in denominator	Observed IRD per 10,000 person-years	95% confidence interval for IRD
Direct Effectiveness						
2007	3	28,249.81	60	37,791.09	-14.81	-10.62, -19.01
2008	23	85,451.55	91	39,447.11	-20.38	-15.51, -25.24
2009	22	131,381.27	74	32,292.04	-21.24	-15.97, -26.51
2010	8	118,708.19	13	18,980.99	-6.18	-2.42, -9.93
Indirect Effectiveness						
2007	60	37,791.09	722	216,767.00	-17.43	-12.74, -22.13
2008	91	39,447.11	722	216,767.00	-10.24	-4.91, -15.56
2009	74	32,292.04	722	216,767.00	-10.39	-4.63, -16.15
2010	13	18,980.99	722	216,767.00	-26.46	-22.01, -30.90
Total Effectiveness						
2007	3	28,249.81	722	216,767.00	-32.25	-29.54, -34.96
2008	23	85,451.55	722	216,767.00	-30.62	-27.95, -33.28
2009	22	131,381.27	722	216,767.00	-31.63	-29.10, -34.16
2010	8	118,708.19	722	216,767.00	-32.63	-30.16, -35.11
Overall Effectiveness						
2007	63	66,040.89	722	216,767.00	-23.77	-20.38, -27.15
2008	114	124,898.67	722	216,767.00	-24.18	-21.23, -27.13
2009	96	163,673.32	722	216,767.00	-27.44	-24.74, -30.14
2010	21	137,689.17	722	216,767.00	-31.78	-29.27, -34.30

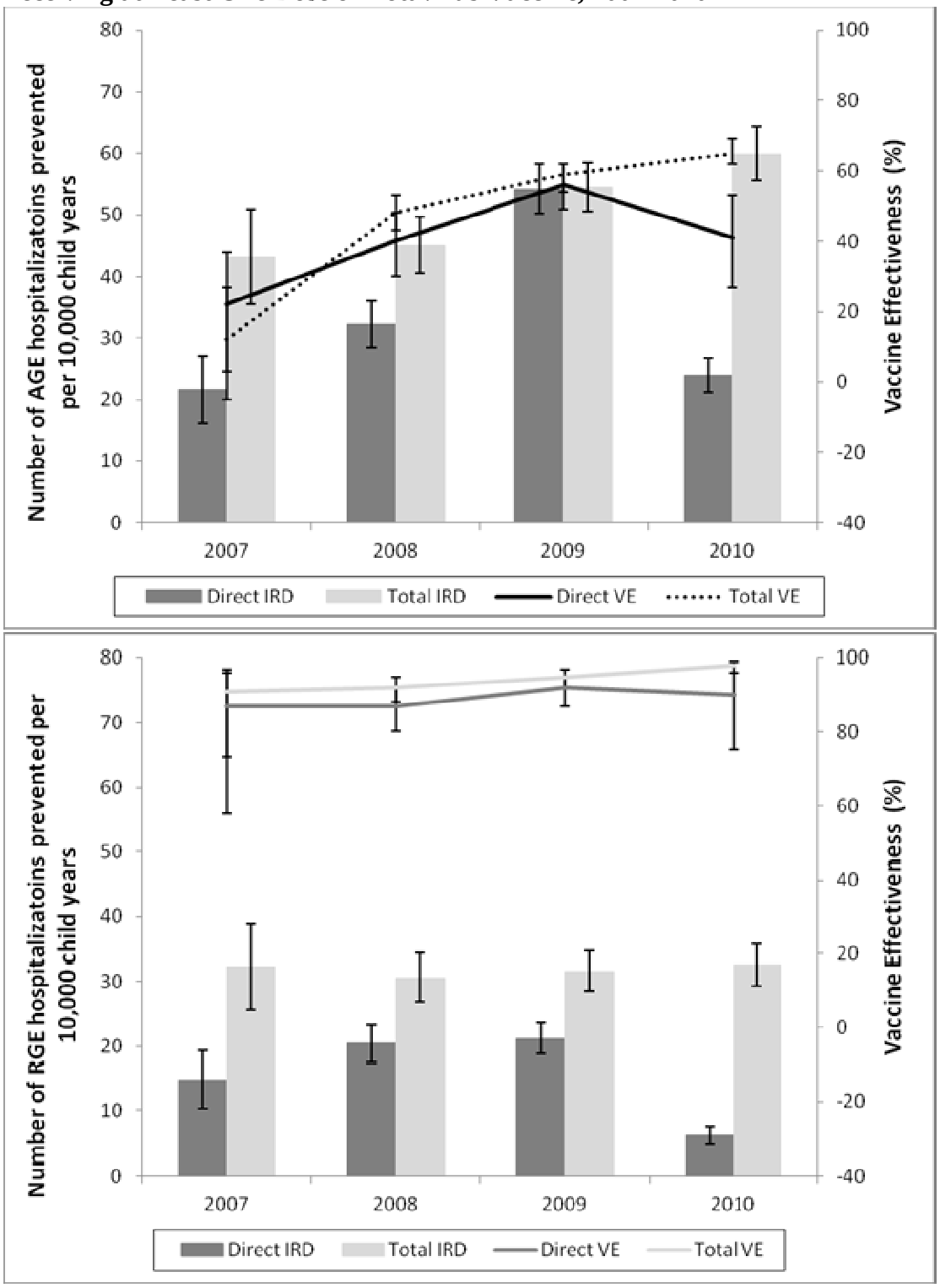
Abbreviations: IRD, incidence rate difference; RGE, rotavirus gastroenteritis

TABLE 8. Absolute Numbers of AGE Hospitalizations Prevented by the Rotavirus Vaccination Program in Commercially Insured US Infants and Children 8 to 20 Months, 2007-2010

Calendar year	Observed number of AGE hospitalizations in numerator	Number of person-years in numerator	Observed number of AGE hospitalizations in denominator	Number of person-years in denominator	Observed IRD per 10,000 person-years	95% confidence interval for IRD
Direct Effectiveness						
2007	142	28,208.94	271	37,696.19	-21.55	-9.64, -33.46
2008	413	85,258.80	317	39,319.23	-32.18	-22.15, -42.21
2009	512	131,095.68	300	32,165.02	-54.21	-43.13, -65.30
2010	398	118,519.67	109	18,932.48	-23.99	-12.69, -35.29
Indirect Effectiveness						
2007	271	37,696.19	2021	216,117.07	-21.62	-12.14, -31.10
2008	317	39,319.24	2021	216,117.07	-12.89	-3.13, -22.66
2009	300	32,165.02	2021	216,117.07	-0.25	-11.56, 11.07
2010	109	18,932.48	2021	216,117.07	-35.94	-24.39, -47.49
Total Effectiveness						
2007	142	28,208.94	2021	216,117.07	-43.18	-33.95, -52.40
2008	413	85,258.80	2021	216,117.07	-45.07	-38.87, -51.27
2009	512	131,095.68	2021	216,117.07	-54.46	-49.16, -59.76
2010	398	118,519.67	2021	216,117.07	-59.93	-54.69, -65.18
Overall Effectiveness						
2007	413	65,905.13	2021	216,117.07	-30.85	-23.56, -38.14
2008	730	124,578.04	2021	216,117.07	-34.92	-29.03, -40.81
2009	812	163,260.70	2021	216,117.07	-43.78	-38.46, -49.10
2010	507	137,452.15	2021	216,117.07	-56.63	-51.44, -61.82

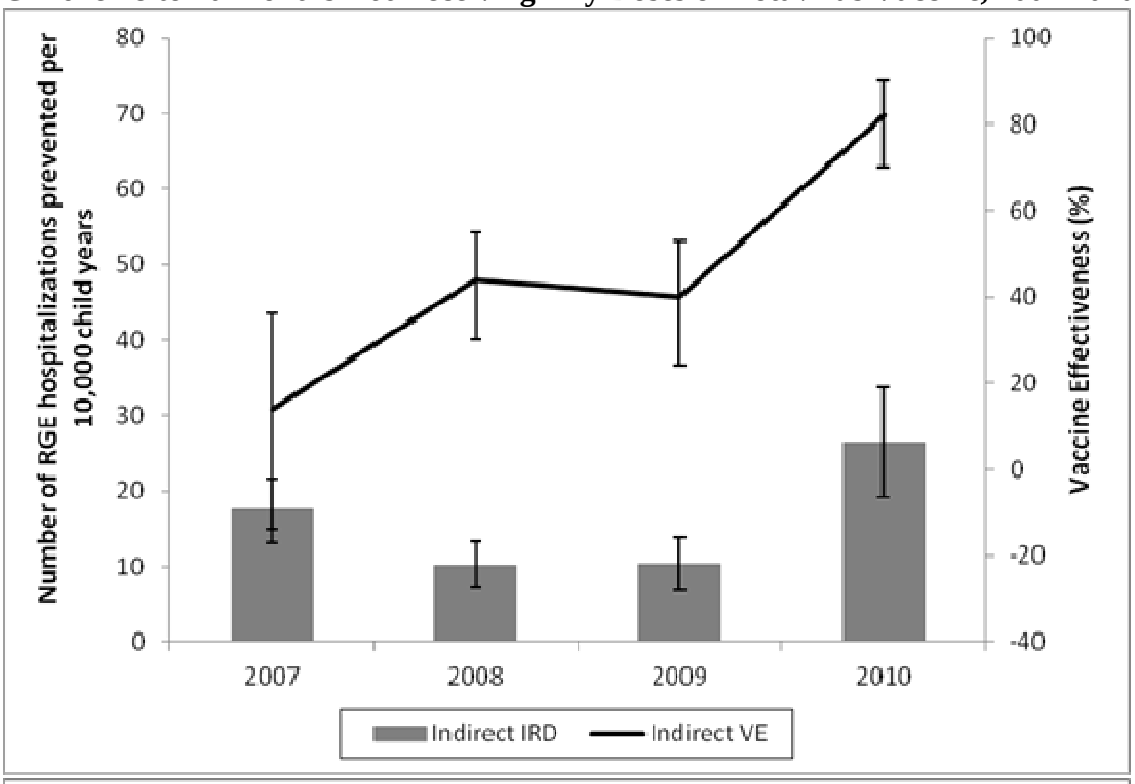
Abbreviations: AGE, acute gastroenteritis; IRD, incidence rate difference

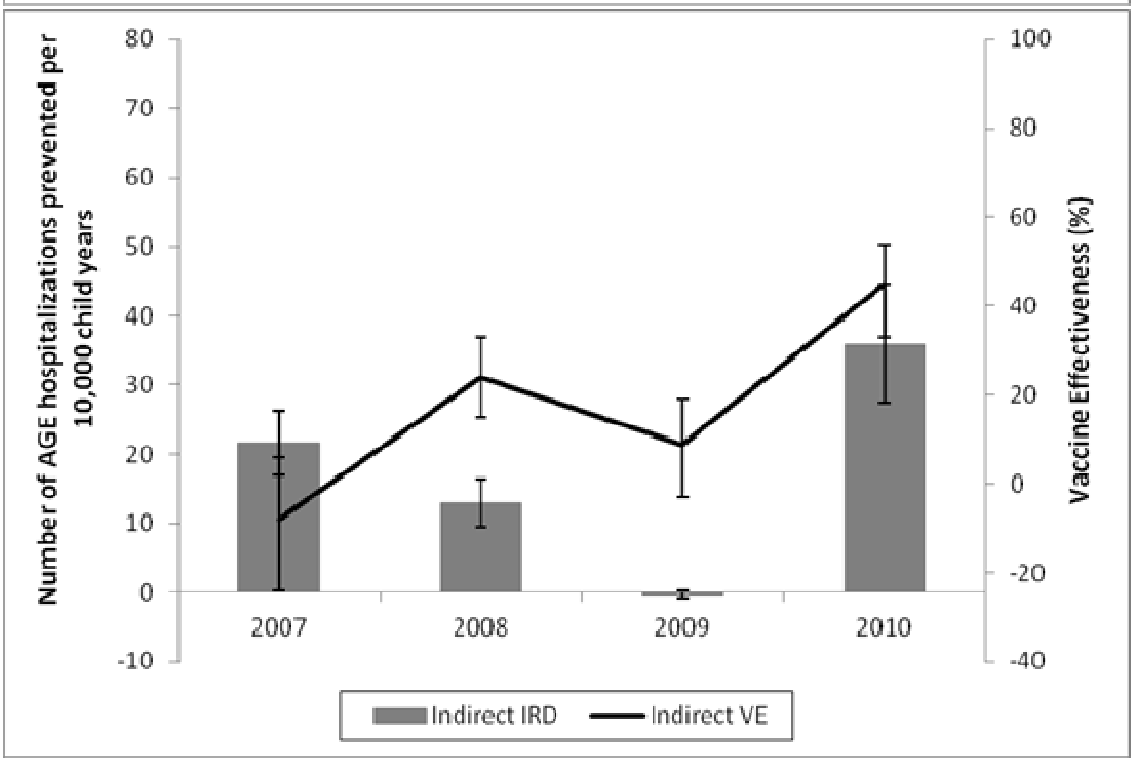
FIGURE 8. Benefit of Rotavirus Vaccine in Preventing RGE and AGE Hospitalizations Among Commercially Insured US Children 8 to 20 Months Receiving at Least One Dose of Rotavirus Vaccine, 2007-2010



Abbreviations: AGE, acute gastroenteritis; RGE, rotavirus gastroenteritis

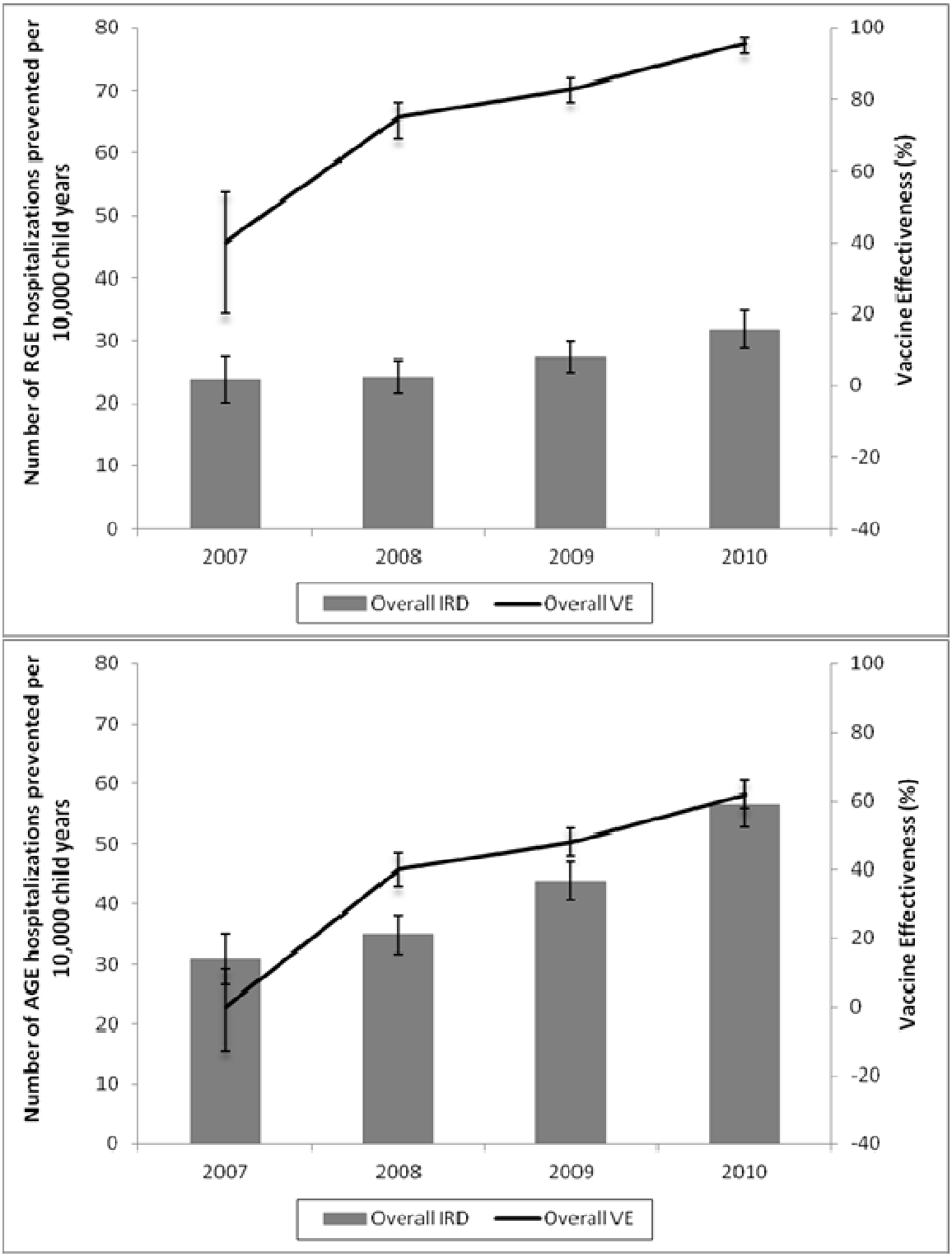
FIGURE 9. Benefit of Rotavirus Vaccine Use in the General Population in Preventing RGE and AGE Hospitalizations Among Commercially Insured US Children 8 to 20 Months Not Receiving Any Doses of Rotavirus Vaccine, 2007-2010





Abbreviations: AGE, acute gastroenteritis; RGE, rotavirus gastroenteritis

FIGURE 10. Public Health Benefit of Rotavirus Vaccine Use in Preventing RGE and AGE Hospitalizations Among Commercially Insured US Children 8 to 20 Months, 2007-2010



Abbreviations: AGE, acute gastroenteritis; RGE, rotavirus gastroenteritis

References

1. Dennehy PH. Acute diarrheal disease in children: Epidemiology, prevention, and treatment. *Infect Dis Clin North Am*. 2005;19(3):585-602. 10.1016/j.idc.2005.05.003.

2. Cortes JE, Curns AT, Tate JE, et al. Rotavirus vaccine and health care utilization for diarrhea in U.S. children. *N Engl J Med*. 2011;365(12):1108-1117. 10.1056/NEJMoa1000446.

3. Parashar UD, Alexander JP, Glass RI, Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention (CDC). Prevention of rotavirus gastroenteritis among infants and children. recommendations of the advisory committee on immunization practices (ACIP). *MMWR Recomm Rep*. 2006;55(RR-12):1-13.

4. Cortese MM, Parashar UD, Centers for Disease Control and Prevention (CDC). Prevention of rotavirus gastroenteritis among infants and children: Recommendations of the advisory committee on immunization practices (ACIP). *MMWR Recomm Rep*. 2009;58(RR-2):1-25.

5. Centers for Disease Control and Prevention (CDC). National, state, and local area vaccination coverage among children aged 19-35 months - united states, 2011. *MMWR Morb Mortal Wkly Rep*. 2012;61:689-696.

6. Centers for Disease Control and Prevention (CDC). National and state vaccination coverage among children aged 19--35 months --- united states, 2010. *MMWR Morb Mortal Wkly Rep*. 2011;60:1157-1163.

7. Centers for Disease Control and Prevention (CDC). National, state, and local area vaccination coverage among children aged 19-35 months --- united states, 2009. *MMWR Morb Mortal Wkly Rep*. 2010;59(36):1171-1177.

8. Kempe A, Patel MM, Daley MF, et al. Adoption of rotavirus vaccination by pediatricians and family medicine physicians in the united states. *Pediatrics*. 2009;124(5):e809-16. 10.1542/peds.2008-3832.

9. U.S. Department of Health and Human Services. Healthy People 2020 Cancer Objectives. . http://www.healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?topicid=5. Updated 2012 August 2. Accessed October 18, 2012.

10. Freed GL, Freeman VA, Clark SJ, Konrad TR, Pathman DE. Pediatrician and family physician agreement with and adoption of universal hepatitis B immunization. *J Fam Pract*. 1996;42(6):587-592.

11. Wendy B. Vaccination with 3-dose paediatric rotavirus vaccine (RotaTeq((R))): Impact on the timeliness of uptake of the primary course of DTPa vaccine. *Vaccine*. 2012. 10.1016/j.vaccine.2012.04.071.

12. Luman ET, Shaw KM, Stokley SK. Compliance with vaccination recommendations for U.S. children. *Am J Prev Med*. 2008;34(6):463-470. 10.1016/j.amepre.2008.01.033.

13. Luman ET, Stokley S, Daniels D, Klevens RM. Vaccination visits in early childhood: Just one more visit to be fully vaccinated. *Am J Prev Med*. 2001;20(4 Suppl):32-40.

14. Wang FT, Mast TC, Glass RJ, Loughlin J, Seeger JD. Effectiveness of an incomplete RotaTeq(R) (RV5) vaccination regimen in preventing rotavirus gastroenteritis in the united states. *Pediatr Infect Dis J*. 2012. 10.1097/INF.0b013e318275328f.

15. Krishnarajah G, Davis EJ, Fan Y, Standaert BA, Buikema AR. Rotavirus vaccine series completion and adherence to vaccination schedules among infants in managed care in the united states. *Vaccine*. 2012;30(24):3717-3722. 10.1016/j.vaccine.2011.12.077.

16. Halloran ME, Struchiner CJ, Longini IM,Jr. Study designs for evaluating different efficacy and effectiveness aspects of vaccines. Am J Epidemiol. 1997;146(10):789-803.

17. Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field. Further observations. Epidemiol Rev. 1988;10:212-41.

18. Schuchat A, Bell BP. Monitoring the impact of vaccines postlicensure: new challenges, new opportunities. Expert Rev Vaccines. 2008;7(4):437-56. (doi: 10.1586/14760584.7.4.437).

19. Parashar UD, Alexander JP, Glass RI, et al. Prevention of rotavirus gastroenteritis among infants and children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006;55(RR-12):1-13.

20. Cortese MM, Parashar UD, Centers for Disease Control and Prevention (CDC). Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2009;58(RR-2):1-25.

21. Hsu VP, Staat MA, Roberts N, et al. Use of active surveillance to validate international classification of diseases code estimates of rotavirus hospitalizations in children. Pediatrics. 2005;115(1):78-82. (doi: 10.1542/peds.2004-0860).

22. Patel MM, Tate JE, Selvarangan R, et al. Routine laboratory testing data for surveillance of rotavirus hospitalizations to evaluate the impact of vaccination. Pediatr Infect Dis J. 2007;26(10):914-9. (doi: 10.1097/INF.0b013e31812e52fd).

23. Desai R, Curns AT, Steiner CA, et al. All-cause gastroenteritis and rotavirus-coded hospitalizations among US children, 2000-2009. Clin Infect Dis. 2012;55(4):e28-34. (doi: 10.1093/cid/cis443).

24. Cortes JE, Curns AT, Tate JE, et al. Trends in healthcare utilization for diarrhea and rotavirus disease in privately insured US children <5 years of age, 2001-2006. Pediatr Infect Dis J. 2009;28(10):874-8. (doi: 10.1097/INF.0b013e3181a653cd).

25. Cortes JE, Curns AT, Tate JE, et al. Rotavirus vaccine and health care utilization for diarrhea in U.S. children. N Engl J Med. 2011;365(12):1108-17. (doi: 10.1056/NEJMoa1000446).

26. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol. 2005;58(4):323-37. (doi: 10.1016/j.jclinepi.2004.10.012).

27. Measuring rurality: rural-urban continuum codes , 2012.

28. Tate JE, Cortese MM, Payne DC, et al. Uptake, impact, and effectiveness of rotavirus vaccination in the United States: review of the first 3 years of postlicensure data. Pediatr Infect Dis J. 2011;30(1 Suppl):S56-60. (doi: 10.1097/INF.0b013e3181fefdc0).

29. Centers for Disease Control and Prevention (CDC). Reduction in rotavirus after vaccine introduction--United States, 2000-2009. MMWR Morb Mortal Wkly Rep. 2009;58(41):1146-9.

30. Centers for Disease Control and Prevention (CDC). Delayed onset and diminished magnitude of rotavirus activity--United States, November 2007-May 2008. MMWR Morb Mortal Wkly Rep. 2008;57(25):697-700.

31. Tate JE, Panozzo CA, Payne DC, et al. Decline and change in seasonality of US rotavirus activity after the introduction of rotavirus vaccine. Pediatrics. 2009;124(2):465-71. (doi: 10.1542/peds.2008-3528).

32. Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med. 2006;354(1):23-33. (doi: 10.1056/NEJMoa052664).

33. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006;354(1):11-22. (doi: 10.1056/NEJMoa052434).

34. Staat MA, Payne DC, Donauer S, et al. Effectiveness of pentavalent rotavirus vaccine against severe disease. Pediatrics. 2011;128(2):e267-75. (doi: 10.1542/peds.2010-3722).

35. Wang FT, Mast TC, Glass RJ, et al. Effectiveness of an Incomplete RotaTeq(R) (RV5) Vaccination Regimen in Preventing Rotavirus Gastroenteritis in the United States. Pediatr Infect Dis J. 2012. (doi: 10.1097/INF.0b013e318275328f).

36. Patel MM, Tate J, Cortese M, et al. The impact of indirect benefits of vaccination on postlicensure vaccine effectiveness estimates: A scenario analysis. Vaccine. 2010;28(50):7987-92. (doi: 10.1016/j.vaccine.2010.09.044).

37. Payne DC, Staat MA, Edwards KM, et al. Direct and Indirect Effects of Rotavirus Vaccination Upon Childhood Hospitalizations in 3 US Counties, 2006-2009. Clin Infect Dis. 2011. (doi: 10.1093/cid/cir307).

38. Lopman BA, Curns AT, Yen C, et al. Infant rotavirus vaccination may provide indirect protection to older children and adults in the United States. J Infect Dis. 2011;204(7):980-6. (doi: 10.1093/infdis/jir492).

39. Tate JE, Mutuc JD, Panozzo CA, et al. Sustained decline in rotavirus detections in the United States following the introduction of rotavirus vaccine in 2006. Pediatr Infect Dis J. 2011;30(1 Suppl):S30-4. (doi: 10.1097/INF.0b013e3181ffe3eb).

40. Pitzer VE, Atkins KE, de Blasio BF, et al. Direct and indirect effects of rotavirus vaccination: comparing predictions from transmission dynamic models. PLoS One. 2012;7(8):e42320. (doi: 10.1371/journal.pone.0042320).

41. Patel MM, Steele D, Gentsch JR, et al. Real-world impact of rotavirus vaccination. Pediatr Infect Dis J. 2011;30(1 Suppl):S1-5. (doi: 10.1097/INF.0b013e3181fefa1f).

42. Ali M, Emch M, von Seidlein L, et al. Herd immunity conferred by killed oral cholera vaccines in Bangladesh: a reanalysis. Lancet. 2005;366(9479):44-9. (doi: 10.1016/S0140-6736(05)66550-6).

43. Nelson EA, Tam JS, Bresee JS, et al. Estimates of rotavirus disease burden in Hong Kong: hospital-based surveillance. J Infect Dis. 2005;192 Suppl 1:S71-9. (doi: 10.1086/431492).

44. Matson DO, Staat MA, Azimi P, et al. Burden of rotavirus hospitalisations in young children in three paediatric hospitals in the United States determined by active

surveillance compared to standard indirect methods. J Paediatr Child Health. 2012;48(8):698-704. (doi: 10.1111/j.1440-1754.2012.02445.x; 10.1111/j.1440-1754.2012.02445.x).

45. Pitzer VE, Viboud C, Simonsen L, et al. Demographic variability, vaccination, and the spatiotemporal dynamics of rotavirus epidemics. Science. 2009;325(5938):290-4. (doi: 10.1126/science.1172330).

46. Hull JJ, Teel EN, Kerin TK, et al. United States rotavirus strain surveillance from 2005 to 2008: genotype prevalence before and after vaccine introduction. Pediatr Infect Dis J. 2011;30(1 Suppl):S42-7. (doi: 10.1097/INF.0b013e3181fefd78).

47. Staat MA, Payne DC, Donauer S, et al. Effectiveness of Pentavalent Rotavirus Vaccine Against Severe Disease. Pediatrics. 2011;128(2):e267-75. (doi: 10.1542/peds.2010-3722).

48. Boom JA, Tate JE, Sahni LC, et al. Effectiveness of pentavalent rotavirus vaccine in a large urban population in the United States. Pediatrics. 2010;125(2):e199-207. (doi: 10.1542/peds.2009-1021).

49. Buttery JP, Lambert SB, Grimwood K, et al. Reduction in rotavirus-associated acute gastroenteritis following introduction of rotavirus vaccine into Australia's National Childhood vaccine schedule. Pediatr Infect Dis J. 2011;30(1 Suppl):S25-9. (doi: 10.1097/INF.0b013e3181fefdee).

50. Martinon-Torres F, Alejandro MB, Collazo LR, et al. Effectiveness of rotavirus vaccination in Spain. Hum Vaccin. 2011;7(7).

CHAPTER V

CONCLUSIONS

A. Recapitulation of overall study aims, findings and degree to which the goals of the doctoral research have been met

1. Determine predictors of rotavirus vaccine initiation and completion.

Comment. The strongest predictors of both rotavirus vaccine series initiation and completion were receipt of DTaP and visiting a pediatrician versus family physician. Since most children who received a rotavirus also received at least one other recommended childhood vaccine (e.g., DTaP), it appears that neither parents nor providers are "cherry-picking" vaccines. Rather, it appears that infants either generally receive the recommended childhood vaccines or do not. This observation is further supported by a post-hoc analysis that found a high correlation between the number of doses of DTaP (one, two, or three) and number of doses of RV5 (one, two, or three) received among infants in our cohort (r=0.76). Since our cohort consisted of infants with private insurance who had at least one outpatient record, failure to access the healthcare system cannot fully explain why some infants did not receive recommended vaccines, such as DTaP or rotavirus. Based on our results, interventions aimed at increasing the coverage of any one childhood vaccine may help increase the coverage and timeliness of other recommended childhood vaccines, assuming that vaccine availability is not an issue. This was shown to be the case for the DTaP vaccine in Australia, where the third dose coverage of DTaP vaccine in a pre-RV5 cohort was 80%, but increased by 5 to 12 percent once the RV5 vaccine was available and widely used.(1)

Education interventions, particularly those targeted at family physicians should be considered. This recommendation is consistent with the results of a 2007 nationally-representative survey of pediatricians and family physicians which found that pediatricians were much more likely to administer the rotavirus vaccine to eligible infants than family physicians, possibly because family physicians were more concerned with vaccine safety and adding additional vaccines to the childhood schedule than pediatricians.(2) Studies examining other vaccines in various populations of infants and young children have also shown that family physicians may be less likely to adopt and may be less knowledgeable about vaccine recommendations than pediatricians.(3)

A priori, we predicted that population size and density of an infant's residence would also be an important predictor of vaccine series initiation and completion. While infants residing in rural and small urban areas were less likely to be vaccinated than those residing in large metropolitan areas in our study, they were also underrepresented which limited study power. A dataset that includes a more geographically diverse cohort of infants is necessary to further explore this factor further.

2. Assess timeliness of rotavirus vaccine administration as per the 2009 Advisory Committee on Immunization Practices (ACIP) guidelines

Comment. Overall, adherence to the 2009 ACIP guidelines for rotavirus vaccine administration was high. Although we compared all years of data (2006 to 2010) to the 2009 ACIP guidelines which are less stringent than the 2006 ACIP guidelines, adherence remained high even when we reanalyzed our data using the 2006 ACIP guidelines (data not shown).

Despite overall high levels of compliance to the 2009 ACIP recommendations, ensuring that infants complete the rotavirus vaccine series could be improved. Other multi-dose vaccines face a similar challenge. Prior to rotavirus vaccine availability, the vaccination histories of over 17,000 children in the 2005 NIS were reviewed, revealing that of the 28% of children not compliant with ACIP recommendations, two-thirds were categorized as such because they were missing doses for multi-dose vaccinations.(4) However, since vaccination coverage has been shown to increase as the number of physician office visits increase, one remedy physicians could consider is vaccinating infants at-risk for missing office visits with RV1 since it requires only two doses to complete the series.(5) However, since identifying infants at-risk for missing office visits can be difficult, this recommendation may only be practical in theory. Furthermore, post-marketing data comparing partial series effectiveness of RV5 to RV1 are limited.(6)

3. Estimate the direct, indirect, total, and overall rotavirus vaccine effectiveness (VE) against rotavirus gastroenteritis (RGE) and acute gastroenteritis (AGE) hospitalizations among those aged 8 to 20 months over the life course of the vaccines

Comment . Receiving one or more doses of RV5 or RV1 was highly effective in preventing RGE hospitalizations in this population of commercially-insured US infants and children aged 8 to 20 months. Direct VE was high across each calendar year, ranging from 87% in 2007 and 2008 to 92% in 2009, and indirect protection increased the VE among the rotavirus-vaccinated by an additional 3 to 8% each calendar year. Overall VE estimates ranged from 40 to 96% each calendar year.

We expected indirect or herd protection against RGE hospitalizations to increase with each successive calendar year from 2007 to 2010, but this was not the case. The calendar

year 2009 had a slightly lower indirect VE estimate than 2008 (44% versus 40%). Although a lack of difference between these indirect VE estimates cannot be ruled out since their confidence intervals overlap, the apparent decline of indirect VE in 2009 is worth further consideration. Not only a decline, but a total absence of indirect protection from the rotavirus vaccine during the 2009 rotavirus season has been observed in other studies, and it has been hypothesized that the low levels of rotavirus activity during the 2008 season allowed unvaccinated children to pass through the season without exposure to wild-type virus until 2009.(7-9)

4. Calculate the absolute rate reductions of RGE and AGE hospitalizations attributable to the rotavirus vaccine or the rotavirus vaccine program in those aged 8 to 20 months

   Comment. Under the assumption of perfect sensitivity and specificity of the RGE ICD-9-CM code, 31 to 33 RGE hospitalizations per 10,000 child-years were prevented in vaccinated children and 10 to 26 RGE hospitalizations per 10,000 child-years were prevented in unvaccinated children in our cohort during each calendar year, 2007- 2010. Failure to account for indirect protection in the rotavirus-vaccinated population underestimated the number of hospitalizations 1.5 to 5.3-fold.

B. Strengths

This dissertation has several strengths. For both the patterns of use and VE study, our population was limited to infants and children with commercial insurance. Since providers of such patients must report the vaccinations they administer in order to receive reimbursement, rotavirus vaccines were likely coded if given, and conversely, likely uncoded if not given. However, to further increase specificity, all CPT vaccine codes were required to have a corresponding date of service, and states with reported universal

vaccination programs that include RV5 or RV1 (Alaska, Idaho, Massachusetts, Maine, North Dakota, New Hampshire, New Mexico, Oregon, Rhode Island, Vermont, Washington, Wisconsin, Wyoming) and were excluded.(10) Thus, although we cannot verify that rotavirus vaccine misclassification was extremely limited, we have strong reason to believe that this was the case.

With regards to the VE study, our study has two important strengths. First, across both time and vaccination status, the five calendar years or periods we examined were generally well balanced on selected covariates which included proxies for health, potential sources of rotavirus infections, and population-level rotavirus vaccination coverage and mixing patterns. Since all cohort members were commercially insured and required to have at least one outpatient record during infancy as well as at least one dose of DTaP, such standards may have led to the relatively good balance between the groups with regards to the measured, and hopefully, unmeasured potential confounders. Second, since we used Cox proportional hazards regression, our analyses inherently adjusted for age and we also stratified by year to account for increasing vaccination coverage and adjusted for month of birth to account for the changing seasonality of rotavirus over the study period. Further adjustment using the covariates we described in Table 1 did not appreciably change our VE estimates so they were not presented. This lack of change was not surprising since our groups seemed reasonably well balanced.

C. Limitations

Our patterns of use analyses are subject to limitations. Many variables potentially predictive of rotavirus vaccine uptake were not available in our data. Further research is needed to examine the effect of potentially relevant predictors, such as race,

ethnicity, family economic status, and physician reimbursement levels. We were unable to validate important estimated dates, such as birth dates and rotavirus vaccination dates. While such misclassifications could affect the results of our analysis that assesses adherence to the 2009 ACIP recommendations, we do not suspect that there was enough misclassification to affect our overall conclusions and they are consistent with the results from another recently published study.(11) As mentioned earlier in the discussion, the infants in our cohorts were not representative of the US infant population; however, our study included nearly 600,000 infants with commercial insurance who may represent the group of infants that most commonly utilizes the rotavirus vaccines.

Our results from the VE study should be interpreted with caution due to four main limitations. First, the RGE ICD-9-CM code likely had low sensitivity which would bias the number of RGE hospitalizations prevented downward. Thus, we conducted sensitivity analyses on the number of RGE hospitalizations prevented assuming 25% and 50% sensitivity of the RGE ICD-9-CM code.(12, 13) These analyses made assumptions that may not have been entirely realistic, including that the sensitivity did not vary over time or between vaccinated and unvaccinated children and that estimates of 25 and 50% sensitivity and 100% specificity were reasonable. AGE ICD-9-CM diagnostic codes were also subject to low sensitivity. A recent study conducted at three US children's hospitals found that only 52% of children hospitalized with AGE received a qualifying diagnostic code at discharge.(14) Fortunately, low sensitivity of RGE or AGE ICD-9-CM codes would not bias VE estimates if specificity was high which was assumed based on research as well as other studies showing similar RGE and AGE hospitalization

patterns as our study.(12, 15-18) Second, we limited the age range of follow-up to infants and children between 8 and 20 months. Some studies suggest that the US rotavirus vaccination program may have increased the mean age at which infants and children are first infected with rotavirus, and thus potentially hospitalized with RGE.(19, 20) If the shift in mean age has been dramatic, the rotavirus vaccines in the later years (e.g., 2010) may appear more effective overall than in the earlier years simply because the burden of RGE hospitalization has shifted to older age groups. A US strain surveillance study of 919 EIA-confirmed RGE cases found that while the mean age of cases was 13.1 and 13.3 months during the 2005-2006 and 2006-2007 rotavirus seasons, the mean age of cases increased to 17.7 months during the 2007-2008 rotavirus season.(20) Despite this potential shift, our study would still accurately document rotavirus VE among 8 to 20 month olds, and since RGE hospitalizations are generally considered most serious in very young children (e.g., <2 years), our study would still have captured many of the most clinically significant cases. Third, our study considered infants receiving any number of doses of rotavirus vaccine as "vaccinated" and did not compare the direct VE of RV5 to RV1 due to the limited number of infants vaccinated with RV1. A few comparative effectiveness studies as well as studies assessing partial rotavirus vaccine effectiveness have been published, and ongoing monitoring should continue to assess these questions.(6, 20-25) Finally, as was the case for our patterns of use study, our VE study may have limited generalizability since it involved only US infants and children with commercial insurance, and did not include those with Medicaid insurance or the uninsured population. However, our study is one of the largest rotavirus

VE studies to-date, and assesses effectiveness in the population of infants and children most likely to receive the rotavirus vaccines in the US.

D. Public Health Implications

Our first study revealed rapid initial uptake of the vaccine after RV5 was first licensed. However, even several years after licensure, many children still did not receive the vaccine or received an incomplete series. Quality improvement efforts should focus on ensuring that (1) infants complete the two-dose series for RV1 and three-dose series for RV5 or a mixed series; (2) family physicians receive the adequate education and support necessary to increase the rates of vaccination among infants in their care; and (3) other recommended infant vaccinations are administered.

In addition to confirming the direct and indirect effectiveness of the rotavirus vaccines, our second study revealed several points to consider when estimating VE both pre- and post-market. Due to the demonstrated importance of indirect VE, we recommend that the indirect impact of vaccines be measured prior to the post-market phase, if possible. This is especially important for candidate vaccines with limited direct VE, but potentially strong indirect VE (e.g., cholera vaccines, rotavirus vaccines in certain developing countries). Using geographic variations in vaccination coverage may help clinical trials measure the indirect impact of vaccinations, and thus provide better estimates of the real-world impact of a vaccine before it is marketed.(26)

If a vaccine has high direct VE, such measurements may only slightly underestimate the total VE which also account for indirect protection among vaccinated persons. However, failing to account for indirect VE may severely underestimate the impact of important public health outcomes, such as the absolute number of RGE hospitalizations

prevented among vaccinated children. For this reason, VE studies should strive to provide both direct and indirect VE estimates, and also report results in the context of absolute benefits

E. Future Directions

Research is ongoing and several exciting studies are planned with potential support from a R21 grant on vaccine safety. First, in an effort to increase generalizability, we plan to conduct a feasibility study using the North Carolina Division of Medicaid Assistance Claims data. Since children with Medicaid insurance automatically qualify for the federally funded Vaccines For Children (VFC) program which limits provider reimbursement for many vaccines, including rotavirus vaccines, to administrative charges, we predict that RV5 and RV1 codes will be underreported in Medicaid claims data. However, since the rotavirus vaccine is the only routinely administered oral vaccine in the U.S., the use of oral vaccine administration codes offers potential opportunities to study patterns of uptake, effectiveness, and safety of the rotavirus vaccines in Medicaid claims data. In addition, although we cannot link MarketScan data directly to patient medical records, we will attempt to externally validate the rotavirus vaccine codes and RGE and AGE codes using the North Carolina Immunization Registry (NCIR) and the North Carolina Disease Event Tracking and Epidemiologic Research Tool (NC DETECT). Finally, we plan to compare the safety of RV5 and RV1 among infants by calculating the relative risks for intussusception and other potential adverse events identified through data mining, and determine whether patients vaccinated on alternative vaccine schedules or failing to complete the vaccine series have an increased risk for adverse events. We predict that small elevated risks of intussusception

immediately following vaccination will be identified in both vaccines, but safety patterns among infants vaccinated by alternative schedules versus the recommended schedule, and infants enrolled in Medicaid versus commercial insurance, will be similar.

References

1. Wendy B. Vaccination with 3-dose paediatric rotavirus vaccine (RotaTeq((R))): Impact on the timeliness of uptake of the primary course of DTPa vaccine. Vaccine. 2012. (doi: 10.1016/j.vaccine.2012.04.071).

2. Kempe A, Patel MM, Daley MF, et al. Adoption of rotavirus vaccination by pediatricians and family medicine physicians in the United States. Pediatrics. 2009;124(5):e809-16. (doi: 10.1542/peds.2008-3832).

3. Freed GL, Freeman VA, Clark SJ, et al. Pediatrician and family physician agreement with and adoption of universal hepatitis B immunization. J Fam Pract. 1996;42(6):587-92.

4. Luman ET, Shaw KM, Stokley SK. Compliance with vaccination recommendations for U.S. children. Am J Prev Med. 2008;34(6):463-70. (doi: 10.1016/j.amepre.2008.01.033).

5. Luman ET, Stokley S, Daniels D, et al. Vaccination visits in early childhood: just one more visit to be fully vaccinated. Am J Prev Med. 2001;20(4 Suppl):32-40.

6. Wang FT, Mast TC, Glass RJ, et al. Effectiveness of an Incomplete RotaTeq(R) (RV5) Vaccination Regimen in Preventing Rotavirus Gastroenteritis in the United States. Pediatr Infect Dis J. 2012. (doi: 10.1097/INF.0b013e318275328f).

7. Payne DC, Staat MA, Edwards KM, et al. Direct and Indirect Effects of Rotavirus Vaccination Upon Childhood Hospitalizations in 3 US Counties, 2006-2009. Clin Infect Dis. 2011. (doi: 10.1093/cid/cir307).

8. Cortes JE, Curns AT, Tate JE, et al. Rotavirus vaccine and health care utilization for diarrhea in U.S. children. N Engl J Med. 2011;365(12):1108-17. (doi: 10.1056/NEJMoa1000446).

9. Lopman BA, Curns AT, Yen C, et al. Infant rotavirus vaccination may provide indirect protection to older children and adults in the United States. J Infect Dis. 2011;204(7):980-6. (doi: 10.1093/infdis/jir492).

10. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol. 2005;58(4):323-37. (doi: 10.1016/j.jclinepi.2004.10.012).

11. Krishnarajah G, Davis EJ, Fan Y, et al. Rotavirus vaccine series completion and adherence to vaccination schedules among infants in managed care in the United States. Vaccine. 2012;30(24):3717-22. (doi: 10.1016/j.vaccine.2011.12.077).

12. Hsu VP, Staat MA, Roberts N, et al. Use of active surveillance to validate international classification of diseases code estimates of rotavirus hospitalizations in children. Pediatrics. 2005;115(1):78-82. (doi: 10.1542/peds.2004-0860).

13. Nelson EA, Tam JS, Bresee JS, et al. Estimates of rotavirus disease burden in Hong Kong: hospital-based surveillance. J Infect Dis. 2005;192 Suppl 1:S71-9. (doi: 10.1086/431492).

14. Matson DO, Staat MA, Azimi P, et al. Burden of rotavirus hospitalisations in young children in three paediatric hospitals in the United States determined by active surveillance compared to standard indirect methods. J Paediatr Child Health. 2012;48(8):698-704. (doi: 10.1111/j.1440-1754.2012.02445.x; 10.1111/j.1440-1754.2012.02445.x).

15. Desai R, Curns AT, Steiner CA, et al. All-cause gastroenteritis and rotavirus-coded hospitalizations among US children, 2000-2009. Clin Infect Dis. 2012;55(4):e28-34. (doi: 10.1093/cid/cis443).

16. Centers for Disease Control and Prevention (CDC). Delayed onset and diminished magnitude of rotavirus activity--United States, November 2007-May 2008. MMWR Morb Mortal Wkly Rep. 2008;57(25):697-700.

17. Centers for Disease Control and Prevention (CDC). Reduction in rotavirus after vaccine introduction--United States, 2000-2009. MMWR Morb Mortal Wkly Rep. 2009;58(41):1146-9.

18. Tate JE, Panozzo CA, Payne DC, et al. Decline and change in seasonality of US rotavirus activity after the introduction of rotavirus vaccine. Pediatrics. 2009;124(2):465-71. (doi: 10.1542/peds.2008-3528).

19. Pitzer VE, Viboud C, Simonsen L, et al. Demographic variability, vaccination, and the spatiotemporal dynamics of rotavirus epidemics. Science. 2009;325(5938):290-4. (doi: 10.1126/science.1172330).

20. Hull JJ, Teel EN, Kerin TK, et al. United States rotavirus strain surveillance from 2005 to 2008: genotype prevalence before and after vaccine introduction. Pediatr Infect Dis J. 2011;30(1 Suppl):S42-7. (doi: 10.1097/INF.0b013e3181fefd78).

21. Staat MA, Payne DC, Donauer S, et al. Effectiveness of Pentavalent Rotavirus Vaccine Against Severe Disease. Pediatrics. 2011;128(2):e267-75. (doi: 10.1542/peds.2010-3722).

22. Boom JA, Tate JE, Sahni LC, et al. Effectiveness of pentavalent rotavirus vaccine in a large urban population in the United States. Pediatrics. 2010;125(2):e199-207. (doi: 10.1542/peds.2009-1021).

23. Buttery JP, Lambert SB, Grimwood K, et al. Reduction in rotavirus-associated acute gastroenteritis following introduction of rotavirus vaccine into Australia's National Childhood vaccine schedule. Pediatr Infect Dis J. 2011;30(1 Suppl):S25-9. (doi: 10.1097/INF.0b013e3181fefdee).

24. Martinon-Torres F, Alejandro MB, Collazo LR, et al. Effectiveness of rotavirus vaccination in Spain. Hum Vaccin. 2011;7(7).

25. Patel MM, Steele D, Gentsch JR, et al. Real-world impact of rotavirus vaccination. Pediatr Infect Dis J. 2011;30(1 Suppl):S1-5. (doi: 10.1097/INF.0b013e3181fefa1f).

26. Ali M, Emch M, von Seidlein L, et al. Herd immunity conferred by killed oral cholera vaccines in Bangladesh: a reanalysis. Lancet. 2005;366(9479):44-9. (doi: 10.1016/S0140-6736(05)66550-6).