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RamyaSree Ramaraju Date

Assessing the Impact of Rotavirus Vaccination on Idiopathic Thrombocytopenic Purpura in the United States

By

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By

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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2019

Abstract

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By: RamyaSree Ramaraju

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Rotavirus vaccination has been extremely effective in reducing rotavirus infections in the United States and has had several non-rotavirus impacts. Idiopathic/Immune Thrombocytopenic Purpura (ITP) is a blood disorder that has been linked with Measles Mumps Rubella vaccination in the past and its association with rotavirus vaccination are currently unknown.

METHODS

The MarketScan Commercial Claims and Encounters Database was utilized to perform a survival analysis on enrollees on the risk of developing ITP based on vaccination status while accounting for covariates such as sex of the enrollee and the enrollee's geographic region. Of 371,422 enrollees from the 2009 MarketScan birth cohort, 292,566 enrollees were eligible for analysis.

RESULTS

Analysis of the data by vaccination status resulted in a hazard ratio of 1.10 with a 95% confidence interval of (95% CI: 0.48, 2.52). When controlling for sex, the hazard ratio was 1.07 (95% CI: 0.47, 2.46) and upon controlling for region, the hazard ratio was 1.10 (95% CI: 0.48, 2.52). The hazard ratios indicate little difference when controlling for the covariates.

CONCLUSION

We found no evidence of correlation between rotavirus vaccination and ITP. Additional studies might be required to more conclusively assess the effect of rotavirus vaccination on ITP.

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We found no evidence of correlation between rotavirus vaccination and ITP. Additional studies might be required to more conclusively assess the effect of rotavirus vaccination on ITP.

BACKGROUND

Rotavirus is a contagious virus that causes acute gastroenteritis and commonly affects infants and young children. Common characteristics of this disease include vomiting and watery diarrhea for three to eight days along with symptoms of fever and abdominal pain. This disease is commonly transmitted through the fecal-oral route, usually by direct contact between people.[1] Rotavirus has been found to be a pathogen affecting children in both industrialized and developing countries. Additionally, other sanitation and hygiene measures have not been effective in protecting against rotavirus.[2]

Rotavirus is one of the major causes of diarrheal disease amongst infants and young children in the United States. Approximately 80% of children in the United States had been infected with rotavirus by the age of 5 years prior to the implementation of the vaccination program for rotavirus in the United States in 2006. Each year between the years of 1990 and the early 2000s, approximately 410,000 physician visits, 205,000-272,000 emergency department visits and 55,000-70,000 hospitalizations occurred due to rotavirus infection among infants and children in the United States.[3,4] As a result, total annual indirect and direct costs attributed to the virus amounted to approximately $1 billion.[5]

The first rotavirus vaccine (RRV-TV, Rotashield) was introduced in 1998 and was licensed and recommended as a routine immunization for infants in the United States. Due to its association with intussusception, RRV-TV was discontinued and withdrawn from the United States market within 14 months after introduction.[6] There are currently two rotavirus vaccines on the market in the United States-RV5 (RotaTeq) and RV1 (Rotarix). RotaTeq is administered to children in a 1-2 month interval in three oral doses commencing from 2 months and continuing through 4 months and 6 months of age while Rotarix is typically administered in two oral doses at 2 and 4 months of age.[7] The Advisory Committee on Immunization Practices (ACIP) does not show preference for one vaccination over another[5]. Both RotaTeq and Rotarix are live-oral vaccines; each of these vaccines is highly effective in preventing severe rotavirus diarrhea and there is a lower risk of rotavirus vaccine-associated intussusception with both of these vaccinations as compared to RRV-TV.[8]

Although there remains a limited risk of intussusception of approximately 1 in 20,000 to 1 in 100,000 US infants who receive the rotavirus vaccine, there are several benefits associated with vaccination.[9] With the introduction of the vaccine in the United States, there has been a significant reduction in hospitalization rates, deaths and overall disease burden. Since RotaTeq was introduced, the following three rotavirus seasons were observed to be shorter and consisted of fewer positive Rotavirus test results.[10] Hospitalizations due to all-cause gastroenteritis in children in the United States younger than 5 years declined by approximately 31%-55% in each year from 2008 through 2012. For hospitalizations due to rotavirus, there was a 63%-94% decline.[11] In addition to reducing hospitalizations, the vaccination has also been linked to societal benefits such as reducing the number of workdays lost for parents due to required in-home care or supervision of children in the hospital.[12] Apart from being a common cause of gastroenteritis in children, rotavirus is also associated with seizures in children.[13] With the introduction of the vaccination, seizure hospitalization risk decreased both in fully and partially vaccinated children.[14,15] Rotavirus vaccination has also been noted to increase herd immunity through interrupting the transmission of rotavirus by preventing infections in individuals that are immunized.[16,17]

Occasionally associated with vaccinations, Idiopathic Thrombocytopenic Purpura (ITP) is a hematologic disorder that leads to excessive bleeding or bruising as a result of low levels of platelets. This condition can affect both children and adults. This disorder is classified in two categories (acute and chronic) and can develop on its own or alongside another condition.[18] Acute ITP occurs commonly in children younger than 10 years of age and is more prevalent during late winter and spring. Chronic ITP is most often seen in adults and adolescents but can also be seen in children. Chronic ITP is generally not associated with seasonality. ITP is one of the more common acquired bleeding disorders that is identified by pediatricians with an incidence of approximately 3.0 to 8.0 per 100,000 children per year and can occur in children following immunizations-commonly after the Measles Mumps Rubella (MMR) vaccination.[19] However, data indicates that ITP with MMR vaccine is very rare and the incidence is about 1 to 3 children for every 100,000 doses of the vaccine.[20,21] Additionally, ITP associated with the MMR vaccination has been observed to be mild and on average resolves within 7 days.[21] Rotavirus infection has also been occasionally linked to incidence of ITP.[22] Although some case

reports have cited rotavirus vaccination as a possible cause of ITP, the causal link is uncertain.[23,24]

Since the introduction of the rotavirus vaccination in the United States in 2006, we have not only seen a decrease hospitalizations and ER visits due to rotavirus thus reducing the economic burden of the infection but also in the cases of rotavirus induced seizures. This study aims to evaluate an additional potential outcome r related to rotavirus vaccination- whether having been administered rotavirus vaccination results in increased risk of ITP or a decreased risk if ITP is caused by natural infection which is prevented by vaccination.

METHODS

Data Source

The IBM® MarketScan® Commercial Database was utilized for analysis. This database consists of de-identified individual level healthcare claims and includes inpatient and outpatient medical information on individuals, their spouses, and dependents with employer-sponsored health insurance in the United States. Data analysis was performed on a birth cohort of 371,422 enrollees from the year 2009 consisting of children with inpatient or outpatient claims records in the MarketScan Claims Database indicating birth in 2009. The follow-up period for each enrollee this study was considered as 2 years from the enrollee's date of birth. The enrollee's exposure status was denoted by whether they had received a vaccination for Rotavirus (RotaTeq or Rotatrix) during the enrollment timeframe. The outcome was denoted by whether the enrollee had an occurrence of ITP during the enrollment timeframe.

Identification of ITP and Vaccination Status

ITP was identified through the International Classification of Diseases, Ninth Revision (ICD-9) code in the inpatient and vaccination records of the MarketScan Database. A vaccinated enrollee was defined as an individual that was vaccinated with RotaTeq or Rotarix during the period of follow-up. If an enrollee was administered at least one vaccination dose, the type of vaccination was derived from vaccination procedure codes (RotaTeq: 90680, Rotarix: 90681). If an enrollee had either of these procedure codes recorded on their inpatient records, they were considered vaccinated. Unvaccinated was defined as an enrollee that was not vaccinated with RotaTeq or

Rotarix during the period of follow-up. ITP was defined as enrollee that had an outcome of ITP in the follow-up period. ITP status was derived from the procedure codes and diagnosis codes (Immune Thrombocytopenic Purpura: 287.31). No ITP was defined as enrollee that did not have an outcome of ITP in the follow-up period. This was derived from the procedure codes and diagnosis codes. If enrollee was not coded with ITP in any of their inpatient procedure codes or diagnosis codes, they were considered as not having ITP.

Survival Analysis Data Setup

The initial birth cohort from 2009 contained 380,553 enrollees. Observations that met the following conditions were excluded from the final survival analysis data set:

- Observations which did not include enrollment information (851 observations removed)
- Observations where date of ITP occurred before date of vaccination (6 observations removed)
- Observations where date of vaccination was recorded as if it occurred before date of birth (747 observations removed)
- Observations where enrollment end date was recorded as if it occurred before date of birth (4,842 observations removed)
- Observations where vaccination date was recorded as if it was before enrollment end date (2,685 observations removed)

The final data set for survival analysis contained 371,422 unique individuals.

Calculation of Enrollee Age for Survival Analysis

Age at Start- The start age was set at 6 months after birth. Enrollees that got the outcome of ITP or individuals that lost enrollment within the first 6 months of birth were excluded from the analysis to start analysis at 6 months of age for every enrollee (time by which each vaccinated enrollee should have received at least the first dose of the vaccination). After excluding individuals that acquired ITP before 6 months of birth or lost enrollment by the first 6 months of birth, 292,566 enrollees were observed for analysis.

Age of ITP-The record with the first occurrence of ITP for each enrollee was maintained and the service date for that inpatient record was used as the date of ITP. Age of ITP was calculated by subtracting the date of birth from the date of ITP occurrence. Enrollees that did not acquire ITP during the follow-up period

2 Year Age-The two-year age for each enrollee was calculated as 730 days.

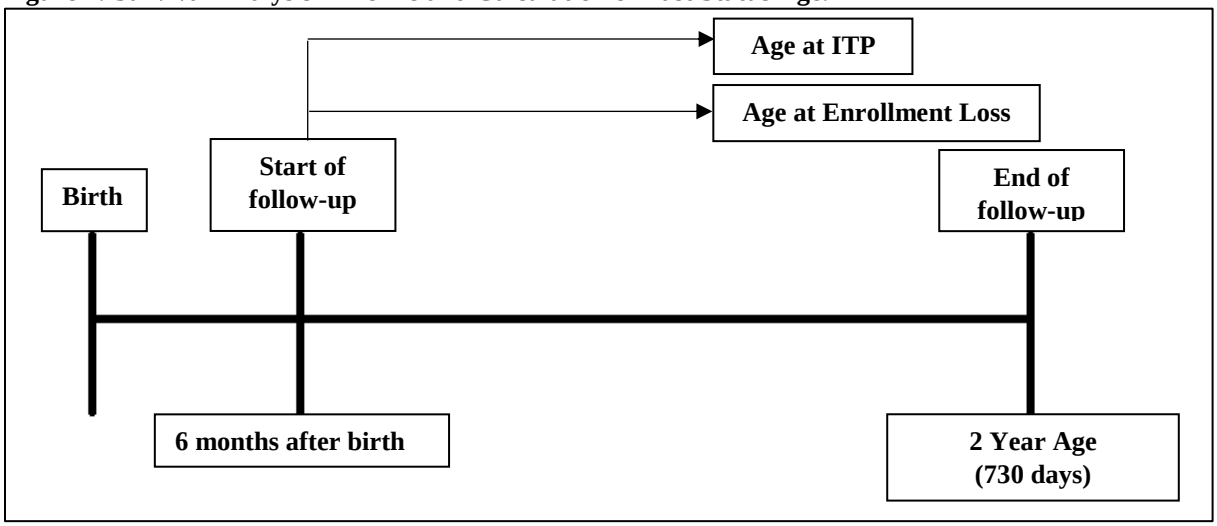
Enrollment End Date-Enrollment end dates were set up with either enrollee losing coverage on the 15th of the month or on the last day of the month depending on the days they were enrolled for each month. If the number of days enrolled for a specific month was less than 15 and the enrollee was not enrolled in the following month, the date of censoring was set as the 15th for the last month in which they were enrolled. Enrollees were censored based on the first time they lost enrollment. If they had insurance coverage, then were not enrolled/lost coverage, and then gained coverage again, they were considered as censored the first time they lost enrollment.

Enrollment End Age- Enrollment end date was calculated by subtracting the enrollee's date of birth from the date at which they lost enrollment.

Last Status Age- Last status age was calculated based on exposure status, outcome status, as well as enrollment loss (Figure 1). If an enrollee acquired ITP and did not lose enrollment, the age at which they had ITP was considered the last status age. However, if ITP was acquired after the enrollee turned two years of age, the lesser of the values between the age at two years (730 days) and age at enrollment loss (if applicable) was considered the last status age.

Follow Up Status-Follow up status was determined by whether the enrollee obtained the outcome of interest within the two-year follow-up period. If individual did not obtain the outcome, survival time was considered censored. Records were censored due to loss of enrollment or not having acquired the outcome within 2 years of the enrollee's date of birth (study end).

Figure 1: Survival Analysis Timeline and Calculation of Last Status Age.



Enrollment loss and ITP occurrence are possible end dates. If ITP occurs before enrollment loss, age at ITP is the last status age. If enrollment loss occurs before ITP, age at enrollment loss is the last status age. If neither occur before end of follow-up, last status age is 730 days.

Statistical Analysis

To determine the association between rotavirus vaccination and ITP, survival analysis based on time-to event to event was conducted on the final dataset. Potential confounders such as sex and region of enrollee were accounted for in the survival analysis. Kaplan Meier curves were plotted for the vaccinated and unvaccinated groups, females and males, and geographic region of enrollees. In order to test for whether a difference exists between the survival curves, the log-rank test was performed for each set of curves. The proportional hazards assumption was tested for the exposure and each covariate through utilizing log-log survival curves and assessing the goodness of fit. The Cox proportional hazards regression model for each covariate was estimated to determine whether there was an increased hazard of ITP for enrollees that were vaccinated to those who were not and for covariates such as sex and region. The hazard ratios are reported with 95 percent confidence intervals (95% CI).

RESULTS

292,566 enrollees from the 2009 birth cohort did not have any reported cases of ITP or lost insurance enrollment within the first 6 months of birth. After the first 6 months of birth, there were a total of 34 (0.01%) cases of ITP amongst the entire study population.

Vaccinated vs. Unvaccinated Enrollees

In Table 1A, we see the proportion of our study population that was vaccinated. The proportions of vaccinated males to females align with the sex distribution in the overall population. The proportion of males to females that were vaccinated was 51.5% to 48.5% which is similar to the distribution of males to females that were unvaccinated as well as the overall population. Puerto Rico was the only region with a higher proportion of individuals who were unvaccinated. However, Puerto Rico represents a very low proportion of the overall population in the analysis. All other regions had more vaccinated individuals than unvaccinated. In the 2009 birth cohort, there was a higher usage of RotaTeq vs. Rotarix. Median age of follow-up did not vary among the vaccinated and unvaccinated groups. The vaccinated group had a slightly higher mean than the unvaccinated group.

Table 1A: Descriptive statistics of MarketScan data for 2009 cohort of 292,566 enrollees after the first 6 months of birth by status of exposure to rotavirus vaccination (RotaTeq and Rotarix).

	Vaccinated (n=227988)	Unvaccinated (n=64578)	Overall (n=292566)
AGE (days)			
Mean (SD)	591 (194)	584 (196)	589 (194)
Median [Min, Max]	730 [181, 730]	730 [181, 730]	730 [181, 730]
SEX			
Female	110669 (48.5%)	31448 (48.7%)	142117 (48.6%)
Male	117319 (51.5%)	33130 (51.3%)	150449 (51.4%)
REGION			
North	38922 (17.1%)	13601 (21.1%)	52532 (18.0%)
North Central	60553 (26.6%)	18708 (29.0%)	79261 (27.1%)
Puerto Rico	4 (0.0%)	13 (0.0%)	17(0.0%)
South	54975(24.1%)	11830 (18.3%)	66805 (22.8%)
West	62668 (27.5%)	17612 (27.3%)	80280 (27.4%)
Unknown	10866 (4.8%)	2805 (4.3%)	13671 (4.7%)
VACCIATION TYPE			
Rotarix	38183 (16.7%)	0 (0%)	38183 (13.1%)
RotaTeq	189805 (83.3%)	0 (0%)	189805 (64.9%)
Missing	0 (0%)	64578 (100%)	64578 (22.1%)

Enrollees with ITP vs. Enrollees without ITP

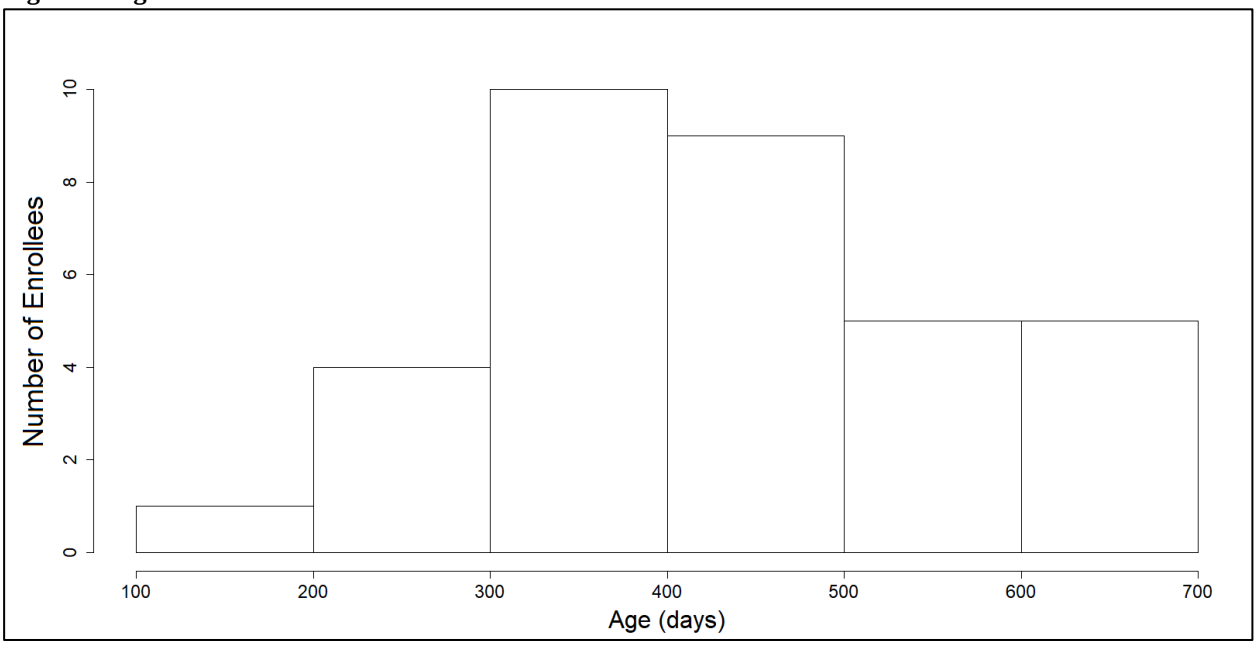
In Table 1B, we see the proportion of ITP across various strata. The incidence of ITP in the overall population was on average approximately 3.87 cases per 100,000 per year for 3 years. ITP is more common amongst males than females even though the birth cohort consists of an almost even split of males and females. ITP was almost evenly split across the various regions of interest apart from the North Central region. Although the West region has the greatest frequency of total enrollees, we observe the highest number of ITP cases from the North Central region. For enrollees from Puerto Rico, there are no reported cases of ITP after 6 months. There was a large proportion of individuals that were vaccinated and got the outcome of ITP. Vaccine coverage among enrollees with ITP was 79.0% and 77.9% among those who did not have ITP and a higher proportion of the cohort was vaccinated than unvaccinated. Age for Table 1B was the last status age. For individuals with ITP, this was the age at which ITP was recorded. For individuals without ITP, this was the age at which they had lost enrollment or 730 days (2 years from date of birth), whichever occurred first.

Table 1B: Descriptive statistics of MarketScan data for 2009 birth cohort of 292,566 enrollees after the first 6 months of birth by outcome status of Idiopathic Thrombocytopenic Purpura (ITP).

	ITP (n=34)	No ITP (n=292532)	Total (n=292566)
AGE (days)			
Mean (SD)	442 (131)	589 (194)	589 (194)
Median [Min, Max]	437 [185, 696]	730 [181, 730]	730 [181, 730]
SEX			
Female	14 (41.0%)	142103 (48.6%)	142117 (48.6%)
Male	20 (59.0%)	150429 (51.4%)	150449 (51.4%)
REGION			
North	6 (17.0%)	52526 (18.0%)	52532 (18.0%)
North Central	15 (44.0%)	79246 (27.1%)	79261 (27.1%)
Puerto Rico	0 (0%)	17 (0.0%)	17 (0.0%)
South	6 (18.0%)	66799 (22.8%)	66805 (22.8%)
West	6 (18.0%)	80274 (27.4%)	80280 (27.4%)
Unknown	1 (3.0%)	13670 (4.7%)	13671 (4.7%)
VACCINATION STATUS			
Unvaccinated	7 (21.0%)	64571 (22.1%)	64578 (22.1%)
Vaccinated	27 (79.0%)	227961 (77.9%)	227988 (77.9%)

34 enrollees had outcome of ITP after the first 6 months (approximately 180 days) of birth. 10 enrollees were excluded from this graphic as they had ITP within the first 6 months of life. There was one case of ITP between the first 180 and 200 days of birth. As seen in Figure 2, a majority of the ITP cases (85%) occurred between the ages of 300 and 500 days. After, 500 days, the instances of ITP leveled off.

Figure 2: Age Distribution of Enrollees with outcome of ITP after first 6 months of birth.



Survival analysis by Exposure: Vaccination Status and Potential Confounders: Sex and Region

Vaccination Status

The survival curves (Figure 3) stratified by vaccination status overlap in multiple areas throughout the follow-up period. The survival curves for the vaccination statuses overlap between 280 and 300 days, 560 and 580 day and 650 and 700 days.

Sex

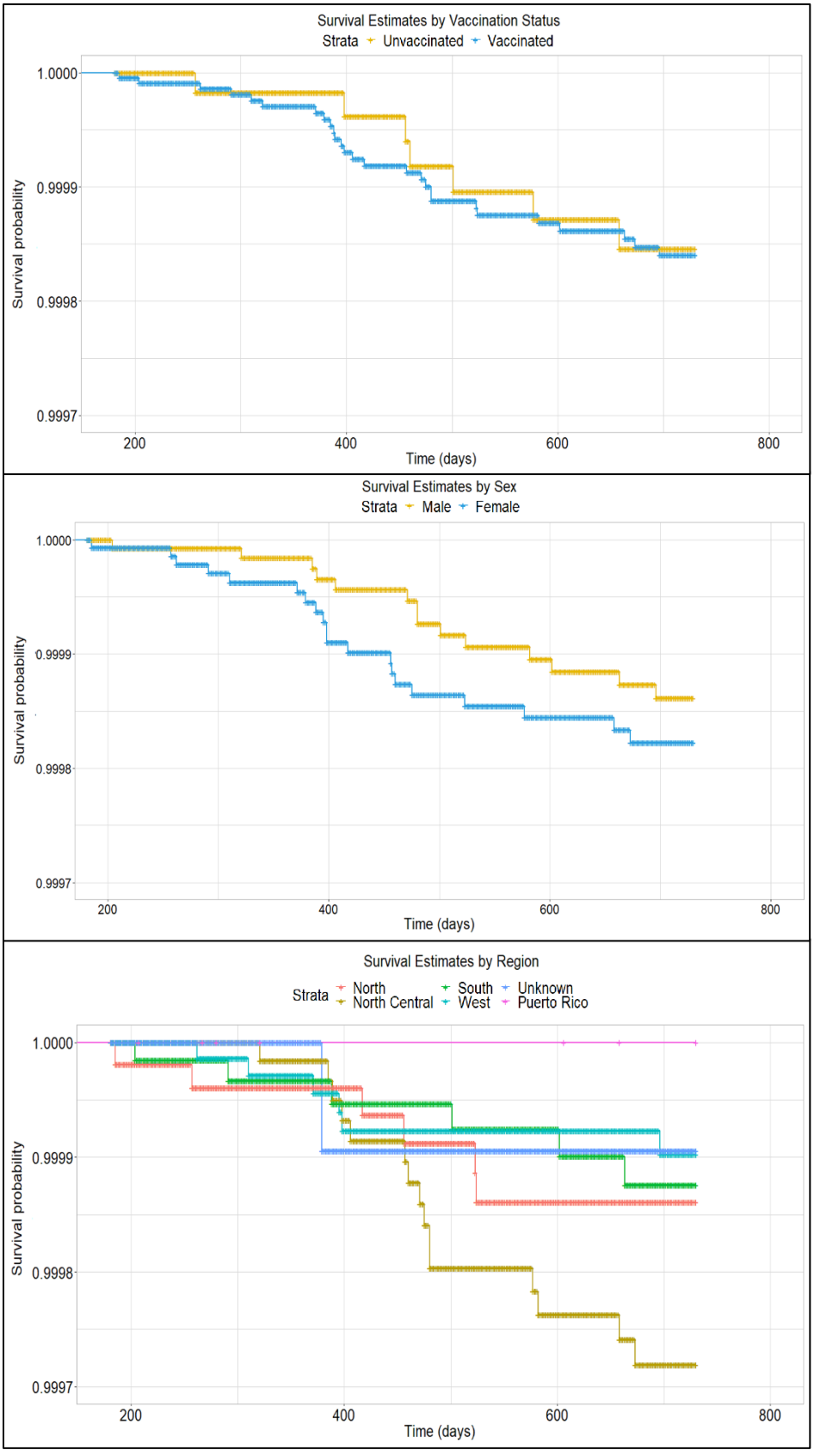
The survival curves for males and females overlap between 200 days and 250 days. After 250 days, the survival curves diverge.

Region

The curve for the North region has a high survival duration from approximately 250 days to 410 days while ending at approximately 510 days. The curve for the North Central region

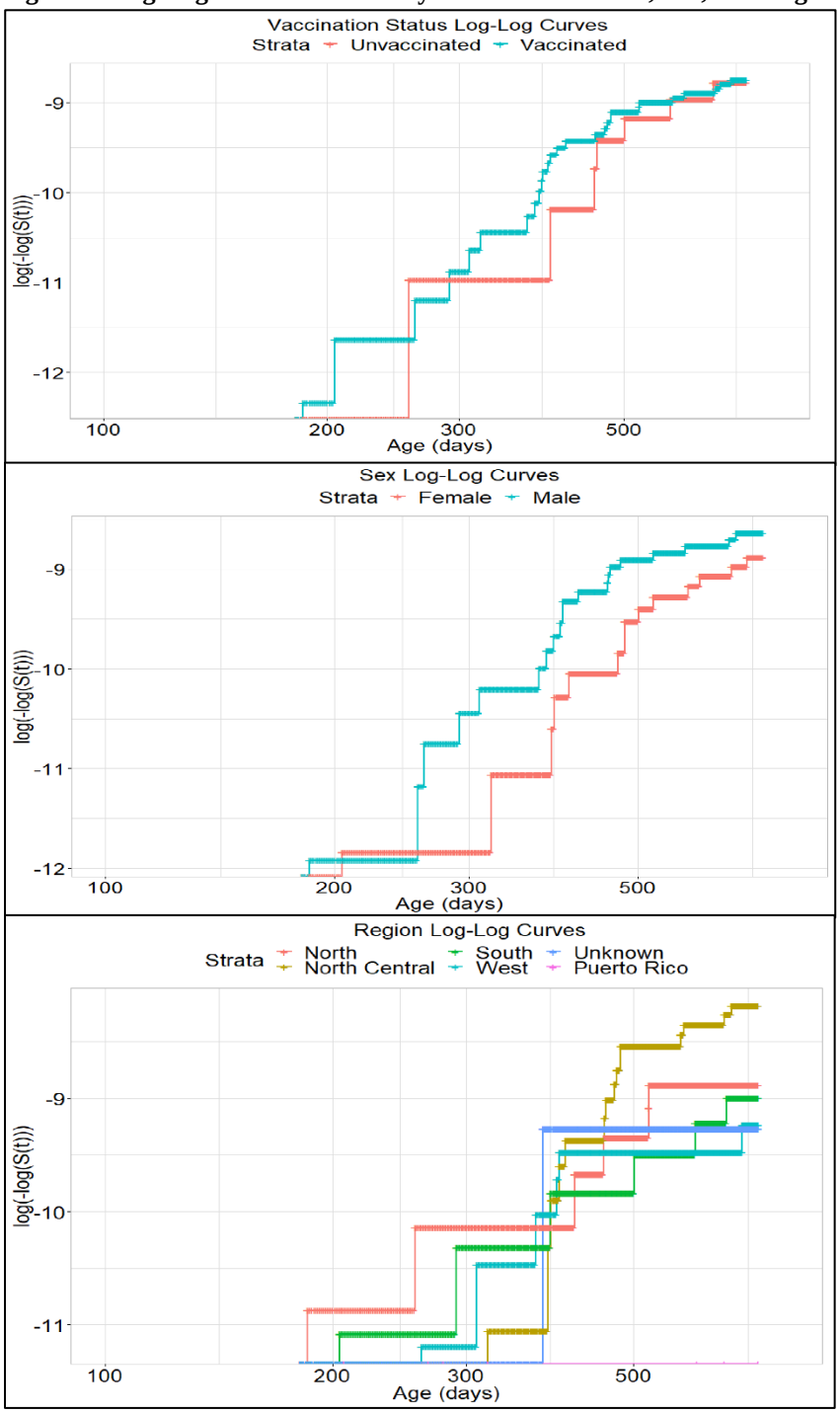
consistently drops throughout the study time and ends around 450 days. The curve for Puerto Rico remains a straight horizontal line as there were no observed cases of ITP in the study time frame. The curve for the Southern region has a few long survival durations: between 200 to 280 days, 280 days to 370 days, 370 days to 490 days, 490 days to 600 days and ending around 660 days. The curve for the western region drops between the study stat time and approximately 390 days but then remains constant from 390 days until 690 days. From 180 days until almost 380 days, the survival curve for the unknown region remains constant and then drops at 380 days and remaining constant until 730 days. There is a significant overlap between the survival curves between 380 days and 410 days.

Figure 3: Kaplan Meier Survival Curves by Vaccination Status, Sex, and Region.



The log-log survival curves for vaccination status cross in multiple areas. The log-log survival curves for sex cross at the beginning of the study time period but then are relatively parallel throughout the study period. The log-log survival curves for geographic region overlap in multiple areas throughout the study period (see Figure 4).

Figure 4: Log-Log Survival Curves by Vaccination Status, Sex, and Region.



At an α-level of 0.05, the log-rank test for vaccination status and the possible confounders, vaccination and geographic region, (Table 3) did not provide strong evidence that survival differs depending on vaccination status, sex or region. Similarly, the goodness of fit test nor the Cox proportional hazards model presented strong evidence of varying survival among the exposure and possible confounders.

Table 3: Log-Rank Test for Vaccination Status and Sex. Goodness of Fit Test, Analysis of Time Dependent Covariates and Estimated Hazard Ratio for Vaccination Status, Sex, and Region.

Variables	Log-Rank Test		Goodness of Fit Test	Cox Proportional Hazards Model	
	Chi-Square	P-value	P-value	P-value	Hazard Ratio[a] (95% CI)
Vaccination Status	0.00	0.90	0.49	0.83	1.10 (0.48, 2.52)
Sex	0.80	0.40	0.09	0.87	1.07 (0.47, 2.46)
Region	6.20	0.30	0.38	0.83	1.10 (0.48, 2.52)

[a]Hazard ratios for sex and region are reported for vaccination status when controlling for the two confounders respectively

Testing the Proportional Hazards (PH) Assumption:

Log-Log survival curves:

As we see an overlap in the log-log survival curves for vaccination status, sex, and region, this indicates that the PH assumption for the exposure and possible confounders might not be met.

Goodness of fit testing:

The goodness of fit tests for vaccination status, sex and region resulted in p-values greater than 0.05. At an α-level of 0.05, these tests are not statistically significant, this indicates that the PH assumption is not violated for these variables when considering the other variables in the model.

DISCUSSION

ITP is an uncommon disorder with the estimated incidence of pediatric ITP at approximately 3.0-8.0 cases per 100,000.[19] The MarketScan data for the 2009 birth cohort aligns with previous studies with a low incidence of ITP. Survival was analyzed on factors such as vaccination status while controlling for sex and geographic region and there appears to be little to no difference in the groups which underwent analysis. In our analysis, we found no evidence that rotavirus vaccination has a markedly significant effect on ITP

With a hazard ratio of 1.10 and a 95% confidence interval of (0.48, 2.52), there was no strong evidence that vaccination status has an effect on ITP. These findings suggest that at any point in the study period, the enrollees that were vaccinated had a 10% higher likelihood to acquire ITP than those who were not vaccinated. With such wide confidence intervals, we have a considerable level of uncertainty surrounding the true level of risk Upon controlling for confounders such as sex and region, we observed similar hazard ratios and confidence intervals. These hazard ratios are marginally larger than 1.00 with wide confidence intervals both when controlling and not controlling for the confounders. After assessing the PH assumption and examining the hazard ratios for the exposure and confounders, the data aligns with previous research in that there is no strong evidence as to whether that rotavirus vaccination has an effect on ITP.[23] Although ITP has also been linked to rotavirus infection,[22] with no strong association between vaccination and ITP, whether vaccination prevents rotavirus induced ITP remains inconclusive.

We note a number of limitations in our study, particularly with the Market Scan Database. The MarketScan claims databases contain biases as the database is not a random sample but instead a convenience sample.[25] The MarketScan data comes largely from large employers so data from firms that are small or medium sized is sparse. Additionally, it is important to note that this database is built through utilizing information from employers, health plans and state Medicaid agencies. Taking into account the types of employer firms that are represented in the database as well as the construction of the data, significant pieces of the general population that may be missed in this dataset. The data also does not provide access to certain types of information and could be missing enrollees of various socio-economic statuses, race/ethnicities, or enrollees who

visit various provider-types. The aforementioned factors may influence both vaccination attitudes as well as propensity for developing ITP.[26] This indicates that the findings may not be generalizable to the population of the United States as a whole.

Another limitation with the MarketScan Database was there were no recorded birthdates for the enrollees. This meant that an enrollee's birthdate needed to be derived based on their inpatient or outpatient records. In some cases, the enrollee's derived birthdate was after their date of vaccination, date of ITP or date of enrollment end. Upon cleaning the data, there were 34 cases of ITP that occurred in the 2009 birth cohort over the two-year study period. Prior to cleaning these records, there were 113 observed cases of ITP meaning there was a loss of 79 possible cases of ITP for analysis. However, we cannot assume that all of these cases would have been included in the study had they met the initial criteria. The regions of the enrollees were also required to be derived based off of the Metropolitan Statistical Area (MSA) of the primary beneficiary. There is a possibility that not all enrollees live with the primary beneficiary so some enrollees might have incorrect geographic codes based on the limited information that exists in the MarketScan database. Due to data limitations, the number of enrollees that were affected by this are however unknown.

As our sample size was cut down due to a lack of clarity on birthdates mentioned above, we lost over half of the ITP cases in the original cohort. Although the 79 cases that were lost may seem like a small number in relation to the larger cohort, keeping low incidence of the disease in mind, we see on average over a three-year period, this would have resulted in a higher incidence of ITP (9.89 cases per 100,000 per year) than what is generally observed. As it presents a slightly higher incidence, it would have been interesting to evaluate whether these additional cases had an effect on the analysis of exposure with respect to the covariates.

This study also started 6 months after the enrollee was born in order to have a same time point for individuals would have received at least one dose of vaccine. It was assumed that by the 6-month period, any given individual would have received at least their first dose of rotavirus vaccination. As RotaTeq is on a 2, 4, and 6 month schedule and Rotarix is on a 2 and 4 month schedule, by 6 months, there is a possibility that some individuals in this study may have

completed their vaccination series. A question remains as to whether number of doses of vaccination (past the first dose) might affect ITP and future research may be needed to assess whether there exists a difference in developing ITP after the first dose through the third for RotaTeq and after the first dose through the second for Rotarix. As acute rotavirus which commonly affects pediatric cases has been linked to seasonality (more commonly seen in winter in springtime),[19] additional research might be beneficial to assess whether the timing of the administration of vaccination doses also has an effect on acquiring ITP.

Rotavirus vaccination is highly effective in preventing rotavirus and has commonly been linked with expected impacts such as significantly reducing hospitalizations, economic burden associated with hospitalizations as well as the unexpected impact of reducing seizures in children. With ITP on rare occasions having been associated with MMR vaccination, upon examining factors such as age and geographic region, rotavirus vaccination does not seem to have an effect on ITP. Regardless of whether it has an association with vaccinations, ITP should not be a limiting factor when considering the use of rotavirus vaccination. However, larger studies in efforts to increase the level of precision with regards to the effect estimate as well as studies assessing number of doses administered, timing, and season of administration of rotavirus vaccine might be required to more conclusively assess the effect of rotavirus vaccination on ITP.

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