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The Impact of Upper Age Limits, Timeliness Adherence, and Program Flexibility on Rotavirus Vaccine Coverage in El Salvador

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Abstract

The Impact of Upper Age Limits, Timeliness Adherence, and Program Flexibility

on Rotavirus Vaccine Coverage in El Salvador

By Eleanor Burnett

In 2006, El Salvador was one of the first countries to introduce a second generation two-dose rotavirus vaccine series in the routine immunization schedule to prevent diarrhea, which is the only vaccine with recommended upper age limits. Previous studies, including a national immunization coverage survey in 2011, have reported lower coverage for rotavirus vaccine than pentavalent vaccine recommended for administration at the same ages; this analysis further investigates reasons for this difference in coverage. To assess the upper age limits' impact on coverage, we analyzed data from 2,250 children ages 24-59 months in a 2011 nationally representative cross-sectional immunization coverage survey. We investigated the proportion of unvaccinated children, reasons for non-vaccination with rotavirus vaccine, timing and co-administration of pentavalent and rotavirus vaccines, and associated factors. There was a 6.3% difference in first dose coverage and a 13.6% difference in second dose coverage between rotavirus and pentavalent vaccines. Receipt of pentavalent vaccine after 104 days of age was associated with not receiving rotavirus vaccine (OR: 0.2). Adherence to the recommended age of administration for the first dose of pentavalent vaccine increased from the 2007 to the 2008 and 2009 birth cohorts (2008 OR: 1.6; 2009 OR: 1.6). Co-administration of rotavirus vaccine with pentavalent vaccine decreased in the 2009 birth cohort. This analysis suggests that adherence to age limits for rotavirus vaccine administration was associated with lower coverage for rotavirus compared to other routine infant immunizations, but may have improved timeliness of vaccination before the nationwide vaccine shortage in 2009. Increased rotavirus vaccination following the shortage indicated flexibility and adaptability of the national immunization program to maintain rotavirus vaccine coverage.

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BACKGROUND

Diarrhea due to rotavirus is one of the leading causes of morbidity and mortality in children under 5 years. In 2008 there were an estimated 453,000 (95% CI 420,000- 494,000) deaths in children less than 5 years of age attributable to rotavirus infection worldwide (1, 2). In 2004, it was estimated that diarrhea accounted for between 13 and 15% of mortality in children less than 5 years of age in the Americas (3). An estimate from countries, including those that had and had not introduced rotavirus vaccine, participating in rotavirus sentinel hospital surveillance in 2006 and 2007 showed that 31.5% of diarrhea hospitalizations were due to rotavirus infection; sentinel hospital surveillance in El Salvador estimated 41% of hospitalizations for diarrhea in children under 5 years were due to rotavirus infection. Between 1 in 3,380 and 1 in 3,452 children less than 5 years of age in El Salvador died due to rotavirus infection, according to estimates from the sentinel hospital surveillance system and the World Health Organization (WHO), respectively. Across the countries in the Americas included in the rotavirus sentinel hospital surveillance analysis, the risk of death due to rotavirus infection ranged from 1 in 2,874 and 2,937 children under 5 years in 2006 and 2007 (4).

The first rotavirus vaccine, Rotashield, was licensed in 1998 and was withdrawn in July, 1999 due to an increased risk of intussusception (5). Intussusception is a potentially fatal bowel obstruction caused by telescoping of the intestines and is the most common cause of bowel obstruction in infants, though deaths due to intussusception are not common in industrialized countries. Studies of the intussusception risk associated with Rotashield reported an increased risk of 37 times and 30 times higher than background 3-7 days after vaccine administration of the first dose. In the 8-14 days following administration of the first dose, the risk was estimated to be 8 times and 4.6 times higher than background levels. The risk was also elevated, though less than with the first dose of rotavirus vaccine, following administration of the second dose (6).

Subsequent analyses also showed an increased risk of intussusception associated with vaccination and evidence that the risk increased with the age of the child at the time of administration (6, 7).

Since 2006, two second generation live orally administered rotavirus vaccines, RotaTeq and Rotarix, have been recommended as a two-dose and three-dose series by WHO (1). These vaccines were tested in large safety and efficacy trials and no increased risk of intussusception was observed (6), though the available RTC's do not have the statistical power to detect very small associations during narrow risk windows (1). Based on the existing evidence, WHO concluded there is insufficient evidence to determine if the first dose of the current rotavirus vaccines is safe after the upper age limits (8). Monitoring of adverse events is ongoing (6,l). The current vaccines have upper age limits of administration of 14 weeks and 6 days of age for the first dose and 32 weeks and 0 days of age for the series, to reduce the risk of intussusception. Rotavirus vaccines are the only vaccine with upper age limits in the routine immunization schedule (1, 9).

In 2012, the WHO Strategic Advisory Group of Experts (SAGE) updated their recommendations for rotavirus vaccine. The new recommendations advise co-administering rotavirus vaccine with the corresponding doses of diphtheria-tetanus-pertussis (DTP) containing vaccine regardless of age, though they reported little benefit to vaccinating children over 24 months of age. Relaxing the upper age limits will allow for vaccination against rotavirus of children who are susceptible to infection but delayed in receipt of immunizations. The new recommendations continue to emphasize adherence to recommended ages of vaccination to reduce the risk of intussusception related to the vaccine (8). The Pan American Health Organization (PAHO) Technical Advisory Group on Immunizations (TAG) also recommended

that countries continue to work towards adherence to the recommended ages of administration, but countries may consider late vaccination of children with rotavirus vaccine at any immunization contact up to one year of age when the burden of disease is high or in areas with limited access (2). One analysis of the impact of relaxing the upper age limits of administration of rotavirus vaccine would prevent an additional 54,087 deaths worldwide in children under 5 years due to rotavirus diarrhea though there would be an excess of 1,226 fatal intussusception cases; the greatest benefit would be in developing countries (6).

There have been two published articles investigating the impact of rotavirus vaccine introduction on rotavirus diarrhea incidence in El Salvador. A study of vaccine effectiveness and diarrheal hospitalizations has shown a positive impact of rotavirus vaccine in El Salvador since introduction in fall 2006. In 2010, a case-control study of monovalent rotavirus vaccine effectiveness in children under 2 years showed a four-fold (OR: 0.24) reduction in hospitalizations due to rotavirus infection among children who received two doses of rotavirus vaccine compared to unvaccinated children., controlling for breastfeeding, premature birth, maternal education, and other socio-economic factors. Vaccine effectiveness was estimated to be 76% (95% CI 64, 84). There was strong adherence to the upper age limits of administration among both cases and controls (10).

In another study using rotavirus diarrhea surveillance data in El Salvador, an overall reduction in rotavirus diarrhea hospitalizations by age group in children under five years between 2006 and 2009 was most significant in children in birth cohorts that had been eligible for vaccination. Diarrhea-related healthcare visits decreased by 48% (47, 48) in 2008 compared with 2006-2007 and by 35% (34, 35) in 2009 compared with 2006-2007. Coverage with the first dose of rotavirus vaccine was estimated between 76% and 89%, by birth cohort (11).

Previous studies have also estimated that coverage with rotavirus vaccine is lower than coverage with pentavalent (diphtheria-tetanus-pertussis-hepatitis B-*Haemophilus infuenzae* type B) vaccine. De Oliveira et al. reported lower coverage of rotavirus vaccine than pentavalent vaccine in 2007 through 2009 in El Salvador. There was a difference in the percentage of children who completed the pentavalent and rotavirus vaccine series of 46.6% in 2007, 11% in 2008, and 29.7% in 2009 (12).

The data used in this study is from an immunization coverage survey completed in El Salvador in 2011. El Salvador is a country in Central America and, in 2011, had a total population of about 6.2 million. Of the total population, 65.3% lived in urban areas; 30.6% was less than 15 years of age. The infant mortality rate was 19 per 1,000 live births (13). In El Salvador, a 2-dose oral rotavirus vaccine series was first introduced in October 2006 after the recommendations by WHO SAGE, and is recommended for administration at 2 and 4 months of age concurrently with injected pentavalent (diphtheria-tetanus-pertussis-hepatitis B-*Haemophilus infuenzae* type B) vaccine and live oral polio vaccine (12). The previously published primary analysis of this survey showed rotavirus vaccine coverage, estimated at 93.7% for the first dose and 86.3% for the second, to be lower than coverage of the corresponding doses of pentavalent vaccine, estimated at 99.9% for both doses. El Salvador experienced a shortage of rotavirus vaccine between July and October of 2009 (14). This secondary analysis was done in collaboration with the El Salvador Ministry of Health to further explore questions raised about reasons for lower rotavirus vaccine coverage.

There have been three previously published studies that investigated the timing of rotavirus vaccine administration, relative to the recommended age of administration. Two studies used data from the Australian Immunization Registry, and the third used the aggregate

number of doses administered in Brazil. No currently published studies investigated the timeliness of rotavirus vaccine using data from individual children in the Americas.

Bissinger (15) and Hull et al. (16) considered adherence to the recommended age of administration for Diptheria-Tetnus-Pertusis (DTP) vaccines scheduled for co-administration with rotavirus vaccine in children born before and after the introduction of rotavirus vaccine. Both analyses found that the proportion of children vaccinated 'on time' with DTP, that is within one month after the recommended age of administration, was higher after the introduction of rotavirus vaccine. Hull et al. also reported a difference in coverage between DTP and rotavirus vaccines. In December 2008, the year of introduction, the difference in coverage was about 15% whereas in December 2009, the difference was just over 5% and remained constant through June 2010.

Flannery et al. (17) used aggregated number of doses administered in children less than one year to compare coverage levels of DTP-containing vaccine doses 1 and 2 compared with the first and second doses of rotavirus vaccine in Brazil. Using an immunization coverage survey of pre-rotavirus vaccine birth cohorts, they found higher coverage of DTP vaccine than rotavirus vaccine and concluded that the higher coverage of DTP is likely due to a delay in administration of the 2 and 4 month vaccines, observed in the pre-rotavirus birth cohort, and that the upper age limit of rotavirus vaccine likely explains its lower coverage.

The articles by Bissinger, Hull, and Flannery all conclude that timeliness of all routine childhood immunization is an important public health goal that maximizes vaccine effectiveness and minimizes the time children are unprotected from disease (15, 16, 17). Hull et al. (16) recommend carefully considering the benefits of increased timeliness with the dangers of not vaccinating children against rotavirus when considering implementing the upper age limit while

Flannery et al. (17) recommend reconsidering the implementation of the upper age limit in order to increase coverage of rotavirus vaccine.

To date, there have been no studies investigating the timeliness of rotavirus vaccine administration or the impact of the upper age limit on rotavirus vaccine coverage using data from individual children in low or middle income settings in the Americas. In this analysis, we investigate the timeliness of rotavirus vaccine and vaccines scheduled for co-administration in El Salvador, provide additional information about the timing of dose administration, consider the impact of age restrictions and shortages of rotavirus vaccine on coverage, and assess factors that are associated with rotavirus non-vaccination.

METHODS

Study Design

This cross-sectional survey of immunization coverage among a nationally representative sample of children ages 24-59 months using a multi-stage stratified cluster sampling design was completed in El Salvador in November and December, 2011, four years after rotavirus vaccine introduction. The methods of the survey were previously described by Suarez-Castenada (8). Briefly, the survey was commissioned by the Expanded Program on Immunization (EPI) of El Salvador and implemented by a local university in collaboration with the Pan-American Health Organization (PAHO). Data were collected by trained surveyors. A list of 262 municipalities and residential areas in 5 regions was used to proportionally select 30 localities and clusters of 17 households within each municipality. Households with no eligible children or that appeared permanently vacant were excluded. Households where no one responded were scheduled for revisits at other times. If the cluster could not be completed with 17 households, the remaining households were selected from the nearest municipality. When there was more than one child in

the target age group in a household, the participant was randomly selected using a random number table. Repeated visits were made to 26 households. Three residential areas that were originally selected were not used due to restricted accessibility and were replaced with three different, randomly selected residential areas. The expected sample size needed was 2,550 children and was calculated for 95% confidence intervals, assuming 80% coverage, with a design effect of two.

Verbal informed consent was obtained from the parents or guardians of the participating children. Routine immunization doses recorded on the individual's vaccination card or recorded at a health facility were considered administered. Children with no written record of pentavalent or rotavirus vaccination were considered unvaccinated, even in the case of parental verbal report. For each missing dose, the parent or guardian was asked to recall the reason it was not administered. Doses with implausible dates were excluded during the data analysis phase. If the first dose of pentavalent or rotavirus vaccine was not recorded on the vaccination card and the second dose of the vaccine was administered and recorded, the first dose was replaced with the information obtained from the second dose and was no longer considered missing. The second dose was re-coded to missing instead. Age at receipt was calculated by subtracting the child's date of birth from the recorded date of administration for each dose of vaccine.

Parents or guardians were also asked to respond to survey questions about other family and community characteristics, such as parental education level, parental marital status, number of people in the household, parental attitudes about immunization, levels of community violence (gangs), presence of community health workers, and accessibility of immunization clinics. These self-reported factors were recorded for each child.

Analytic Methods

The outcome of interest is rotavirus vaccine administration status (1= successfully administered, 0= not administered). For this investigation, the primary exposure variables were categorical measures of the timeliness in administration of first and second doses of pentavalent vaccine and the child's year of birth. To reflect national policy and facilitate comparisons between the doses, timeliness for both vaccines were categorized using the recommended upper age limits for rotavirus vaccine of 104 days for the first dose and 223 days for the series. Exact timeliness definitions for each category are detailed in Table 1.

SAS v9.3 (Cary, NC) was used for all statistical analysis and accounts for the multistage stratified cluster design. Percentages were calculated for selected self-reported family and community characteristics by child's year of birth and percentage. Confidence intervals were calculated for timing of pentavalent and rotavirus vaccination. We used both logistic and Cox regression models in which predictor doses were categorized as administered before or after the upper age limit. Logistic regression models were developed for rotavirus vaccination status predicted by the timing of the corresponding dose of pentavalent vaccine and year of birth, the timeliness of pentavalent vaccination predicted by socio-economic factors, and co-administration patterns predicted by socio-economic factors and year of birth. Confounding was assessed using the backwards change in estimate approach (18).

In the time-to-event analysis using Cox regression, children were considered eligible for each dose of vaccine from the time of birth. Children without a written record of the vaccine of interest were censored at their age at the time of the survey. For the second dose of vaccine, children were considered vaccinated if the child had a written record for the first and second doses of vaccine; children who were missing either dose in the series were censored. The results

are presented in graphs plotting one minus the proportion of unvaccinated children by age in months. These images were generated using R (3.0) survey method survival analysis package.

To calculate hypothetical coverage, we assumed that had there not been a shortage of vaccine, all of the children whose caregiver's reported lack of vaccine as the reason for rotavirus non-vaccination would have been vaccinated against rotavirus. For each birth cohort, we summed the number of children observed to have received the first or second dose of rotavirus vaccine with the number of children whose caregiver reported non-vaccination for that dose due to lack of vaccine. We then divided this sum by the number of children in the birth cohort to obtain the estimated rotavirus vaccine coverage had vaccine supply not been a factor in vaccination.

Similarly, we assumed that had there been no upper age limits, all of the children who did not receive a rotavirus vaccine dose and received the corresponding pentavalent vaccine after the upper age limit would have been vaccinated against rotavirus. We summed the children who had an observed first dose of rotavirus vaccine with the number of children who were observed with the first dose of pentavalent vaccine administered after 104 days of age and divided the total by the number of children in each birth cohort to estimate the impact of the upper age limit on first dose coverage. For the second dose of rotavirus, we summed children who had an observed second dose rotavirus vaccine with children who received the second pentavalent dose after 223 days of age and had an observed the first dose of rotavirus or received the first dose of pentavalent after 104 days of age to estimate the impact of the upper age limits on second dose coverage.

This survey was reviewed by the national and PAHO ethical committees and considered non-research. This analysis was approved by Emory University's Institutional Review Board (IRB).

RESULTS

There were 2,550 children between 24 and 59 months of age enrolled from all five health regions [Table 2]. No caregiver refused to participate in the survey. Three communities were replaced due to inaccessibility and two children were mistakenly replaced when no immunization records were available, though their families reported both children were vaccinated. The individual, family, and community characteristics of the participating children are similar across birth cohorts, with the exception of parental education level (chi square p value=0.03). No child was completely unvaccinated. Data was obtained from a vaccination card for 94.4% of children; health facility records were found for the remaining children. The survey included children born in late 2006 but they were excluded from the analysis because they were eligible for rotavirus vaccine administration during the period of introduction (n=55).

More children had not received the first and second doses of rotavirus vaccine as compared to pentavalent vaccine. Overall, 93.6% (92.2, 95.1) of children received the first dose of rotavirus vaccine, ranging from 90.6% to 95.3% by birth cohort (chi square=14.9, $p<0.001$) [Table 3]. Across birth cohorts, 86.2% (84.0, 88.3) of children completed the two dose rotavirus vaccine series, with no statistically significant difference by year of birth. Of the children who received the first dose of rotavirus vaccine, 7.5% did not receive the second dose. In the 2007 and 2008 birth cohorts, all of the children included in the survey received the first and second doses of pentavalent vaccine; 99.7% (99.3, 100.0) of children received the first dose of pentavalent vaccine and 99.4 (98.7, 100.0) received the second dose in the 2009 birth cohort (chi

square= 5.7, p=0.06). The children who did not receive pentavalent vaccine were excluded from all models. Overall, there was a 6.3% difference in first dose coverage and a 13.6% difference in second dose coverage between rotavirus and pentavalent vaccines.

The effect of upper age limits on rotavirus vaccine coverage

Among children who did not receive the first dose of rotavirus vaccine (n=156) [Table 4], 18.9%, 13.3%, and 32.4% received the first dose of pentavalent vaccine after 104 days in the 2007, 2008, and 2009 birth cohorts, respectively. Among children who did not receive the second dose of rotavirus vaccine (n=331), 69.1%, 34.8%, 36.4% had not received a first dose of rotavirus vaccine in the 2007, 2008, and 2009 cohorts, respectively.

In a crude logistic regression model to assess the timing of first pentavalent dose as a categorical predictor of first rotavirus vaccination status [Table 5; Model 1 in Appendix], children were less likely to be vaccinated with the first dose of rotavirus vaccine if their first dose of pentavalent was administered after 104 days of age (OR: 0.2, 95% CI 0.1, 0.3). Year of birth and maternal education were not confounders of this relationship of the relationship between late pentavalent vaccine administration and rotavirus vaccination status [Model 2].

Also from Table 5, we fit a model (Model 3) to assess the timing of the second pentavalent dose as a predictor of rotavirus vaccine second dose vaccination status. The results showed that children were less likely to receive the second dose of rotavirus vaccine if the second dose of pentavalent vaccination was administered after 223 days of age (OR: 0.1, 95% CI: 0.1, 0.2). After controlling for year of birth, first rotavirus vaccination timing, and maternal education (Model 4), this relationship was not found to be statistically significant (OR: 0.6, 95% CI: 0.2, 1.7).

Based on cumulative incidence curves, the probability of vaccination and uptake for the first dose of rotavirus vaccine appears to be lower for children who received a first dose of pentavalent vaccine after 104 days of age (n=134), visualized in Figure 1b, as compared with children who received a timely (n=2,365) first dose [Figure 1a]. For the second dose of rotavirus, the probability of vaccination and timeliness for children who received a second dose of pentavalent vaccine after 223 days of age (n=76), visualized in Figure 1d, is lower as compared with children who received a timely (n=2,456) second dose [Figure 1c].

Using a Cox Proportional Hazard Model, we found that the administration of pentavalent vaccine before 104 days of age was statistically significantly predictor of the first dose of rotavirus vaccine in a time-to-event model, after controlling for year of birth (HR: 1.2, 95% CI: 1.1, 1.3) [Table 6; Model 5]. In a model of time to rotavirus vaccine second dose administration, controlling for categorical rotavirus vaccine first dose administration and birth cohort [Model 6], pentavalent timing was not found to be a statistically significant predictor (HR: 1.1, 95% CI: 0.9, 1.2). Socio-economic status variables, including maternal education, were not confounders in either model, based on the all possible subsets backwards elimination method to assess a change in estimate.

Had there been no upper age limits of administration, first dose rotavirus vaccine coverage would have been from 92.6% to 96.9% by year of birth; second dose rotavirus vaccine coverage would have ranged from 90.9% to 94.5% [Table 7].

Co-Administration

In comparing the dates of administration [Table 8], we found that 73.0% (69.6, 76.5), 80.1% (77.0, 83.1), and 63.2% (58.9, 67.5) of children received their first doses of rotavirus and pentavalent vaccines on the same date in the 2007, 2008, and 2009 birth cohorts, respectively.

Overall, 6.9% (5.8, 8.1) of children received the first dose of rotavirus vaccine and the second dose of pentavalent vaccine on the same date, ranging from 3.9% to 10.6% by birth cohort. A substantial proportion of children in all three birth cohorts received the first dose of rotavirus vaccine in a separate visit from both the first and second doses of penvalent vaccine, with 11.1% (86, 13.7), 10.9% (8.7, 13.0), and 21.5% (18.1, 24.8) in the 2007, 2008, and 2009 birth cohorts, respectively.

Because oral polio vaccine (OPV) is also a live oral vaccine, we considered whether children who were not co-administered the first rotavirus vaccine with the first or second doses of pentavalent vaccine also received OPV on a different date. Among children who received the first rotavirus vaccine on a different date than both doses of pentavalent vaccine, 90.7% received the first doses of pentavalent and oral polio vaccine (OPV) on the same date, indicating that these children did not have a contraindication to oral vaccine on the date of the first pentavalent visit.

Also shown in Table 8, overall, 64.5% (61.9, 67.0) of children received their second dose of rotavirus and pentavalent vaccines on the same date, ranging from 56.9% to 68.9% by birth cohort. In the 2007 and 2008 cohorts, 2.5% (1.4, 3.7) and 2.1% (1.1, 3.1) of children received their second dose of rotavirus vaccine and their third dose of pentavalent vaccine on the same date, respectively, while 7.9% (5.4, 10.4) did in the 2009 birth cohort. In the 2007 and 2008 birth cohorts, 16.5% (13.8, 19.3) and 14.2% (11.5, 16.9) of children received their second dose of rotavirus on a different date then both the second and third doses of pentavalent, while 22.4% (19.2, 25.5) did in the 2009 cohort. Among children who received the second rotavirus vaccine on a different date than both doses of pentavalent vaccine, 90.4% received the second doses of pentavalent and OPV on the same date.

In a crude polytomous logistic regression model with year of birth predicting the co-administration pattern of first dose of rotavirus vaccine[Model 7], children born in 2007 were more likely than the 2008 birth cohort to receive the first dose of rotavirus vaccine with the second dose of pentavalent vaccine (OR: 0.6, 95% CI: 0.3, 0.9), instead of receiving the first dose of both rotavirus and pentavalent vaccines on the same date [Table 9]. The 2007 and 2008 birth cohort did not have different experiences receiving the first dose of rotavirus vaccine in a separate visit. Children born in 2009 were more likely than children born in 2007 to receive the first dose of rotavirus vaccine and the second dose of pentavalent vaccine in the same visit (OR: 1.9, 95% CI: 1.3, 2.7) and to receive the first dose of rotavirus vaccine in a separate visit from both pentavalent vaccine doses (OR: 2.2, 95% CI: 1.6, 3.0). Socio-economic factors were not found to be confounders.

In a crude model with year predicting co-administration of pentavalent vaccine with the second dose of rotavirus vaccine [Model 8], the 2007 and 2008 birth cohorts did not experience different patterns of second dose rotavirus vaccine co-administration [Table 9]. Children born in 2009 were more likely to receive the second dose of rotavirus vaccine and the third dose of pentavalent vaccine in the same visit (OR: 3.7, 95% CI: 2.1, 6.6), rather than the second doses of rotavirus with the second dose of pentavalent vaccine in the same visit, and to receive the second dose of rotavirus vaccine in a separate visit from both the second and third doses of pentavalent vaccine (OR: 1.6, 95% CI: 1.2, 2.1) as compared with children born in 2007. We found SES factors and the co-administration of the first dose of rotavirus vaccine to be confounders [Model 9].

Adherence to recommended ages of administration

The percent of children who received timely doses of rotavirus vaccine increased between 2007 and 2008 [Table 3]; in 2009, this pattern was disrupted. 1.4% (0.9, 2.0) of all children received an early first dose of rotavirus vaccine (administered before 42 days of age), differential by birth cohort (p=0.03) and 0.4% (0.1, 0.7) of children received an early second dose of rotavirus vaccine (administered before 70 days of age), with no statistically significant difference by birth cohort. Timely administration of the first dose of rotavirus vaccine (administered from 42 to 90 days of age) ranged from 66.1% (61.8, 70.4) to 80.3% (77.2, 83.4) by birth cohort (p<0.001); timely series completion (administered from 70 to 150 days of age) ranged from 58.4% (54.3, 62.6) to 69.6% (66.1, 73.1) by birth cohort (p<0.001). Overall, 4.6% (3.7, 5.6) of children received a delayed first rotavirus vaccine dose (administered from 91 to 104 days of age), ranging from 3.6% to 6.5% by birth cohort (p=0.01), and 18.3% (16.7, 19.9) received a delayed second dose of rotavirus vaccine (administered from 151 to 223 days of age), ranging from 14.1% to 25.2% by birth cohort (p<0.001). 15.0% (13.6, 16.7) of children received a late first dose of rotavirus (administered after 104 days of age), ranging from 9.0% to 22.1% by birth cohort (p<0.001), while 2.4% (1.8, 3.0) received a late second dose of rotavirus vaccine (administered after 223 days of age), by birth cohort from 2.3% to 4.7% (p=0.03).

The majority of children in all three birth cohorts received their first and second doses of pentavalent vaccine ‘on time’ [Table 3]. Overall timely coverage for the first dose of pentavalent was 89.9 (88.6, 91.3), with no statistically significant difference by year of birth. Timely vaccination of the second dose ranged from 81.7% (78.6, 84.7) to 87.4% (85.2, 89.7) by birth cohort (chi square=7.8, p=0.02). Second doses of pentavalent administered from 151 to 223 days of age ranged from 9.7% (7.7, 11.7) to 15.4% (12.5, 18.3) by birth cohort (chi square 11.6,

p=0.003). Second pentavalent doses administered after 223 days of age ranged from 2.3% (1.1, 3.5) to 4.7% (3.0, 6.5) by birth cohort (chi square=6.9, p=0.03).

The probability of vaccination and timing of administration for the first dose of pentavalent vaccine, shown in an inverse Kaplan Meier (cumulative incidence curve) time-to event plot [Figure 2a, 2b, 2c], appear comparable across birth cohorts, with the 2008 birth cohort showing slightly more adherence to the recommended age of administration, shown with the grey box. The probability of vaccination and timing of administration for the second dose of pentavalent vaccine, visualized in Figures 2d-2f, also are comparable across birth cohorts, with slightly improved adherence to the recommended age in the 2008 birth cohort.

Categorizing the timeliness of first doses of pentavalent vaccine [Model 10], there was an improvement in timely administration in the 2008 birth cohort (OR: 1.6; 95% CI 1.6, 1.7) and in the 2009 cohort (OR: 1.6; 95% CI 1.6, 1.7) as compared to the 2007 cohort, controlling for maternal education. For categorical timeliness of the second dose of pentavalent vaccine [Model 11], there was an improvement in the 2008 birth cohort (OR: 1.1; 95% CI: 1.0, 1.1) and a decrease in the 2009 birth cohort (OR: 0.7; 95% CI: 0.68, 0.73) as compared to the 2007 cohort, controlling for maternal education and categorical timing of the first dose of pentavalent vaccine. Urban residence, maternal employment status, and number of residents in the household were not found to be confounders in either model.

Vaccine shortages and rotavirus vaccine coverage

For children missing both the first and second doses of rotavirus vaccine, the majority of parents or guardians with unvaccinated children reported the reason was lack of vaccine at the time of their visit [Table 9]. The parents reported not knowing why the vaccine was not administered as the second most common reason for non-vaccination.

In a crude logistic model of year of birth as a predictor of first rotavirus vaccination status [Model 12], children born in 2007 were less likely to receive the first dose of rotavirus vaccine than children in the 2008 and 2009 birth cohorts (2008 OR: 1.9, 95% CI: 1.3, 2.8; 2009 OR: 2.2 95% CI: 1.5, 3.2) [Table 5]. Pentavalent timing and maternal education were not confounders of this relationship. The odds of receiving two doses of rotavirus vaccine were not statistically significantly different between the birth cohorts in a model of birth cohort predicting second dose rotavirus vaccination status [Model 13]. After controlling for second pentavalent dose timing, first rotavirus dose timing, and maternal education as confounders [Model 14], children born in 2008 and 2009 were less likely to receive the second dose of rotavirus vaccine than children born in 2007 (2008 OR: 0.3 (0.2, 0.5); 2009 OR: 0.5 (0.3, 0.9)).

The probability of vaccination and uptake of the first dose rotavirus vaccine, shown in a cumulative distribution curve, is comparable in the 2007 and 2008 birth cohorts [Figures 3a and 3b]; there is a similar probability of vaccination but less adherence to the recommended age of administration in the 2009 cohort [Figure 3c]. For the second dose of rotavirus, the 2007 and 2008 birth cohorts are similar to each other [Figures 3d and 3e]; the 2009 birth cohort shows slightly higher probability of vaccination but less adherence to the commended age of administration [Figures 3f].

Had there been no shortages of vaccine, first dose rotavirus vaccine coverage could have been 96.8% to 99.4% and second dose rotavirus vaccine coverage could have ranged from 95.8% to 97.3% by birth cohort [Table 7].

Analyzing the number of doses administered by calendar month, there was an unexpected increase in absolute number of doses administered in this survey population in November 2009, compared to both the expected doses, based on dates of birth, and observed doses administered

in previous years [Figure 4]. For the second dose of rotavirus vaccine, there is an unexpected increase in doses administered in January 2010, two months after the increase in first doses [Figure 5]. The rotavirus vaccine shortage lasted from July to October 2009.

DISCUSSION

This analysis of data from an immunization coverage survey of the first three birth cohorts after rotavirus vaccine introduction in El Salvador showed that children who were administered pentvalent vaccine administration after 104 days of age were 5 times less likely to receive the first dose of rotavirus vaccine. Because of rotavirus vaccine shortages during this time period, availability of vaccine, operationalized by birth cohort, was also a predictor of rotavirus vaccination status. Adaptability, seen in co-administration patterns, and diligent follow-up, seen in the unexpected increase in doses administered following the shortage, demonstrate that the immunization program in El Salvador was flexible in its handling of the rotavirus vaccine shortages. As a result, the impact on rotavirus vaccine coverage was minimal. We also observed some improvement timing of pentavalent vaccine administration across birth cohorts as the rotavirus vaccine program matured. Close monitoring of rotavirus vaccine coverage, timeliness, and availability will be important going forward.

Children who received pentavalent vaccine after 104 days of age were less likely to receive the first rotavirus vaccine, suggesting strong adherence by vaccinators to the upper age limit recommendations. No association between pentavalent vaccine timing and the second dose of rotavirus vaccine was observed after controlling for maternal education, year of birth, and timing of the first dose of rotavirus vaccine. For the first dose of rotavirus vaccine, the upper age limits are an important factor in the observed lower coverage than the first dose of pentavalent vaccine. Flannery et al. (17) hypothesized that pentavalent vaccination timing in the pre-

rotavirus vaccine period would predict rotavirus vaccine coverage in program with good adherence to the recommended upper age limits of administration for rotavirus vaccine. They used aggregated number of doses administered in children less than one year to compare coverage levels of DTP-containing vaccine doses 1 and 2 compared with the first and second doses of rotavirus vaccine in Brazil. Using an immunization coverage survey of pre-rotavirus vaccine birth cohorts, they found higher coverage of DTP vaccine than rotavirus vaccine and concluded that the higher coverage of DTP is likely due to a delay in administration of the 2 and 4 month vaccines and that the upper age limit of rotavirus vaccine likely explains its lower coverage. Our findings are consistent with previously published hypotheses that the recommended upper age limits for rotavirus vaccine cause lower coverage as compared with other vaccines scheduled for co-administration (1, 6, 17).

When forecasting new vaccine introduction, it is often assumed that a newly introduced vaccine will quickly have the same coverage level as established vaccines recommended for the same ages (12). In this survey, rotavirus vaccine had lower coverage than pentavalent vaccine over the three years following introduction, though first dose rotavirus vaccine coverage was improving by birth cohort. We also found that the proportion of second pentavalent doses that were administered after 223 days of age decreased from the 2007 cohort to the 2008 and 2009 cohorts, as the program had matured; modeling results showed improvement in timeliness for the first dose of rotavirus vaccine across the birth cohorts. Previous studies by Hull et al. and Bissinger found an association between rotavirus vaccine introduction and improved timeliness of other vaccines between pre-rotavirus vaccine birth cohorts and post-rotavirus vaccine introduction birth cohorts in Australia and hypothesized that the upper age limits of rotavirus vaccine led to increased adherence to the recommended immunization schedule (15, 16). Hyde et

al. (19) also found that new vaccine introductions can strengthen service delivery in existing routine immunization programs.

Our results also highlight challenges of new vaccine introduction, including shortages. The results of this survey show that the immunization program in El Salvador was flexible in its handling of the rotavirus vaccine shortages, resulting in a minimal impact on coverage in 2009, through adaptability in co-administration and diligent follow-up observed in months following the national stock out. In the survey from El Salvador, other rotavirus vaccine shortages likely also played a role in lower and less timely coverage of rotavirus vaccine.

This study had several limitations. First, the survey did not include cohorts before the rotavirus vaccine was introduced and so we were unable to draw conclusions about the association between rotavirus introduction and the timeliness of routine infant immunizations. The vaccine shortage also limited our ability to look at improvements in timeliness across birth cohorts. Although the availability of the vaccine was identified as a primary reason for non-vaccination, we were unable to verify information about local immunization stock or consider provider attitudes towards immunizations and contraindications to immunization for individual children. There were some limitations in the sample due to replacement of three inaccessible municipalities and two children. Finally, this rotavirus vaccine introduction situation was unique to El Salvador's immunization program, though it can provide information for other countries considering introducing rotavirus vaccine into their routine infant immunization schedule.

This study also has several strengths. This survey included three birth cohorts of children eligible for rotavirus and pentavalent vaccines with documentation of the dates of vaccine administration. As receiving pentavalent vaccine was nearly universal, there is access to immunization services in this strong program. Because the immunization and community and

family factors information were individually linked, we were able to assess associations based on individual information, rather than ecological and aggregated information. As a nationally representative survey, the results are generalizable within these birth cohorts in El Salvador. The sample size was also quite large, yielding estimates that were stable and relatively precise.

Our findings add to the limited body of literature about the use of rotavirus vaccine, with a limited period for valid administration, and its impact on timing and coverage, which may be helpful to other country programs considering introducing this vaccine. It also adds to the growing number of analyses looking at vaccination timeliness and adherence to recommended ages of administration. El Salvador, and other countries that have or will imminently introduce new vaccines, should continue to carefully monitor availability of vaccine, vaccination coverage, and timeliness of administration.

CONCLUSIONS

In this analysis of a nationally representative coverage survey of children in El Salvador, we found that children who were administered the first dose of pentavalent vaccine after the upper age limit of administration for the first dose of rotavirus vaccine were less likely to receive the first dose of rotavirus vaccine. This supports the hypothesis that the upper age limits contribute to lower rotavirus vaccine coverage.

Over the first two years after rotavirus vaccine introduction, that is from the 2007 to 2008 cohorts, we observed increased adherence to the recommended ages of administration for pentavalent and rotavirus vaccines. This supports our hypothesis that new vaccine introduction can improve overall routine immunization program performance and that the upper age limits of administration may play a role in increasing adherence.

In the 2009 birth cohort, adherence to the recommended ages of administration for rotavirus vaccine and co-administration of rotavirus vaccine with pentavalent vaccine decreased as compared to the previous years, although overall coverage with rotavirus vaccine did not decrease in this birth cohort. This shows that during a nationwide shortage of vaccine that year, the program continued to prioritize rotavirus vaccination by relaxing adherence to the upper age limits and encouraging adaptability in co-administration. We also observed an increase in doses of rotavirus vaccine administered in the months following the shortage, showing diligent follow-up by the vaccinators and a prioritization of high rotavirus coverage.

FUTURE DIRECTIONS

This analysis of vaccination coverage in three birth cohorts in El Salvador immediately following the introduction of rotavirus vaccine contributes to the understanding of the impact of the use of rotavirus vaccine with upper age limits on routine infant immunization systems. In two previous studies using data from the Australian immunization registry, the impact of introduction of rotavirus vaccine on the timeliness of vaccines scheduled for co-administration was considered in pre- and post- rotavirus vaccine cohorts. This was not possible in our study because the survey population did not include a birth cohort prior to rotavirus introduction for comparison. To better understand the impact of rotavirus vaccine introduction on routine immunization systems, future research should compare cohorts from before and after rotavirus vaccine introduction. To date, research of rotavirus vaccine timeliness has been limited to data from individually linked children in Australia and aggregated data in Brazil. Other settings and systems should be included when considering questions around new vaccine introduction, especially with rotavirus vaccine as WHO now recommends all countries should introduce it to their national routine infant immunization schedule.

One of the articles from Australia also showed a decrease in the difference in coverage in the two years following rotavirus vaccine introduction. In this study we also observed changes in patterns and timeliness of administration in 2009, which limited our ability to assess trends in timeliness of administration with program maturity. Changes in overall immunization coverage and timeliness of administration of rotavirus vaccine and vaccines scheduled for co-administration may increase with program maturity. As more countries introduce rotavirus vaccine, additional data will become available to consider this question.

Future research should also further consider how the upper age limits may be limiting rotavirus vaccine coverage, as has been hypothesized in the literature and was found in our

analysis, though this was limited due to the patterns and timeliness of administration in 2009. As other researchers have shown, there is great potential to prevent morbidity and mortality due to rotavirus diarrhea in children less than 5 years of age and the upper age limits of administration prevent some children who are vulnerable to infection from receiving the vaccine. Additional studies could help quantify the number of children impacted by the upper age limits and characterize children at risk for delayed vaccination.

While this survey did include some information about caregiver attitudes toward immunization, the questions were both limited and general. Qualitative research questions may consider other factors impacting differential rotavirus vaccine and DTP coverage by asking questions specific to rotavirus vaccine, such as attitudes about co-administration of two oral vaccines. It is also important to consider provider attitudes towards new vaccines and their capacity to adapt schedules and co-administration as appropriate in future research.

Finally, researchers should continue to consider measures of timeliness when assessing immunization programs. As methods continue to be appropriated from other fields, immunization researchers should consider the interdependence of doses in the same series and if this interdependence exists between antigens when answering questions about vaccination timeliness and associated factors. This information can help immunization programs better plan for and meet the needs of children susceptible to vaccine preventable diseases and their families.

TABLES

Table 1. Definitions of timeliness by vaccine.

		Recommended age	Invalid	Valid		
			Too early	Timely	Delayed	Late
Rotavirus Vaccine	**Dose 1**	2 months	<42 days of age	42-90 days of age	91-104 days of age	>104 days of age
	Dose 2	4 months	<70 days of age or <28 days from previous dose	70-150 days of age	151-223 days of age	>223 days of age
Pentavalent Vaccine	**Dose 1**	2 months	<42 days of age	42-90 days of age	91-104 days of age	>104 days of age
	Dose 2	4 months	<70 days of age or <28 days from previous dose	70-150 days of age	151-223 days of age	>223 days of age

Table 2. Selected characteristics of surveyed children, their families and communities. El Salvador, 2011

		Year of Birth							
		2007		2008		2009			
		n	%	n	%	n	%	Chi-Square	
Gender	Female	387	47.9	428	49.0	385	46.7	0.7638	p=0.68
Marital Status	Partnered/Married	652	80.3	702	80.2	651	78.9	2.4093	p=0.88
	Divorced/Separated	22	2.9	24	3.0	17	2.3		
	Single	124	15.9	143	15.8	137	17.5		
	Widow/er	8	0.8	8	1.0	7	1.3		
Parental Education Level	None	96	11.8	80	8.5	54	6.7	17.064*	p=0.03
	1st-6th grade	268	32.1	315	36.1	275	33.4		
	7th-9th grade	223	26.7	235	26.3	220	26.1		
	High School	172	23.2	196	23.3	200	25.6		
	Post Secondary	47	6.3	51	5.7	63	8.2		
Parental Employment Status	Homemaker	560	68.6	587	66.9	549	67.1	2.6432	p=0.85
	Employed	234	29.8	275	31.5	247	31.0		
	Unemployed	10	1.3	12	1.3	15	1.8		
	Retired	2	0.3	3	0.3	1	0.1		
Number of people in the household	2	13	1.6	11	1.2	3	0.3	10.6036	p=0.10
	3 to 5	490	60.0	553	61.3	501	58.9		
	6 to 9	259	32.5	263	30.3	251	32.8		
	10 or more	44	5.9	50	7.1	57	7.9		
Primary Mode of Transportation	Foot	439	53.6	462	50.6	392	47.1	11.9895	p=0.15
	Bus	243	31.7	275	33.3	300	38.2		
	Personal Vehicle	53	6.3	64	7.6	61	7.8		
	Taxi	21	2.7	20	2.1	17	2.1		
	Other	50	5.8	56	6.4	42	5.0		
Area of residence	Urban Area	363	47.7	443	51.3	364	46.7	3.9151	p=0.14
Presence of Organized Crime	Yes	131	17.2	143	18.1	122	19.2	0.9822	p=0.61
Region	Central	154	14.4	184	15.6	162	14.8		
	Metropolitan	152	24.2	179	26.0	161	26.1		
	Occidental	169	22.8	175	22.0	155	21.2		
	Oriental	161	22.4	181	22.7	160	21.6		
	Paracentral	170	16.1	158	13.7	174	16.3		

*p<0.05

Table 3. Timing and coverage of rotavirus and pentavalent vaccines by birth cohort among children born in 2007-2009. El Salvador, 2011

			Total		Year of Birth 2007		2008		2009		Chi Square	
			n	% (CI)	n	% (CI)	n	% (CI)	n	% (CI)		
Dose 1	Rotavirus	Early[1]	36	6.4 (4.9, 7.8)	16	1.9 (1.0, 2.8)	15	1.6 (0.8, 2.5)	5	0.6 (0.1, 1.1)	7.0428	p=0.03
		Timely[2]	1,839	72.8 (70.5, 75.1)	577	71.5 (68.0, 74.9)	711	80.3 (77.2, 83.4)	551	66.1 (61.8, 70.4)	19.921	p<0.001
		Delayed[3]	115	4.6 (3.7, 5.6)	31	3.6 (2.3, 4.9)	33	3.9 (2.6, 5.1)	51	6.5 (4.5, 8.5)	8.9058	p=0.01
		Late[4]	349	14.8 (13.1, 16.5)	108	13.7 (11.0, 16.4)	73	9.0 (6.9, 11.2)	168	22.1 (18.4, 25.8)	35.5575	p<0.001
		Not administered	156	6.4 (4.9, 7.8)	74	9.4 (6.9, 11.8)	45	5.2 (3.2, 7.1)	37	4.7 (3.0, 6.3)	14.8752	p<0.001
	Pentavalent	Early[1]	48	1.7 (1.2, 2.3)	19	2.1 (1.1, 3.1)	18	2.0 (1.1, 2.8)	11	1.1 (0.4, 1.7)	3.85	p=0.15
		Timely[2]	2,246	89.9 (88.5, 91.3)	711	88.2 (85.9, 90.5)	803	91.1 (89.1, 93.1)	732	90.6 (88.4, 92.8)	4.9148	p=0.09
		Delayed[3]	67	2.5 (1.9, 3.2)	21	2.5 (1.4, 3.7)	24	2.7 (1.6, 3.8)	22	2.4 (1.3, 3.4)	0.4289	p=0.81
		Late[4]	132	5.7 (4.6, 6.9)	55	7.2 (5.2, 9.2)	32	4.3 (2.8, 5.7)	45	5.9 (3.9, 7.9)	3.7818	p=0.15
		Not administered	2	0.1 (0.0, 0.2)	0	0	0	0	2	0.3 (0.0, 0.7)		
Dose 2	Rotavirus	Early[5]	10	0.4 (0.1, 0.7)	1	0.1 (0.0, 0.3)	5	0.6 (0.0, 1.2)	4	0.5 (0.0, 1.0)	5.5664	p=0.06
		Timely[6]	1,643	65.1 (62.7, 67.6)	542	67.1 (63.6, 70.6)	622	69.6 (66.1, 73.1)	479	58.4 (54.3, 62.6)	13.94	p<0.001
		Delayed[7]	450	18.3 (16.6, 19.9)	128	15.6 (12.9, 18.4)	120	14.1 (11.6, 16.7)	202	25.2 (22.0, 28.4)	25.7346	p<0.001
		Late[8]	61	2.4 (1.8, 3.0)	29	3.6 (2.3, 5.0)	7	0.9 (0.2, 1.5)	25	3.0 (1.8, 4.2)	11.5632	p=0.003
		Not administered	331	13.8 (11.7, 15.9)	106	13.6 (10.6, 16.5)	123	14.8 (11.6, 18.0)	102	12.9 (10.0, 15.7)	2.5203	p=0.28
	Pentavalent	Early[5]	15	0.5 (0.2, 0.9)	5	0.6 (0.1, 1.1)	5	0.6 (0.1, 1.0)	5	0.5 (0.1, 1.0)	0.0830	p=0.96
		Timely[6]	2,118	84.5 (82.7, 86.3)	684	84.6 (81.9, 87.4)	773	87.4 (85.2, 89.7)	661	81.7 (78.6, 84.7)	7.7583	p=0.02
		Delayed[7]	285	11.7 (10.2, 13.1)	81	10.1 (7.8, 12.4)	80	9.7 (7.7, 11.7)	124	15.4 (12.5, 18.3)	11.6127	p=0.003
		Late[8]	74	3.1 (2.2, 4.0)	36	4.7 (3.0, 6.5)	19	2.3 (1.1, 3.5)	19	2.4 (1.3, 3.5)	6.9057	p=0.03
		Not administered	3	0.2 (0.0, 0.4)	0	0	0	0	3	0.6 (0.0, 1.3)		

[1]Administered before 42 days of age
[2]Administered from 42 to 90 days of age
[3]Administered from 91 to 104 days of age
[4]Administered after 104 days of age
[5]Administered before 70 days of age
[6]Administered from 70 to 150 days of age
[7]Administered from 151 to 223 days of age
[8]Administered after 223 days of age

Table 4. Self-reported and observed reasons for missed rotavirus doses 1 and 2 among children born in 2007-2009 who did not receive 1 or more doses of rotavirus vaccine. El Salvador, 2011

			Total		Year of Birth 2007		2008		2009	
			n	%	n	%	n	%	n	%
Self- reported	Rotavirus Dose 1	No vaccine available	113	70.8	48	63.2	33	72.1	32	84.1
		Other reason	43	29.2	26	36.8	12	27.9	5	15.9
		No reason given	0	0	0	0	0	0	0	0
	Rotavirus Dose 2	No vaccine available	251	73.7	72	65.9	98	77.0	81	77.7
		Other reason	72	23.9	32	31.3	23	21.6	17	19.0
		No reason given	8	2.4	2	2.9	2	1.3	4	3.3
Observed	Rotavirus Dose 1	Penta 1 administered before 104 days of age	33	20.8	14	18.9	6	13.3	12	32.4
	Rotavirus Dose 2	Rota 1 not administered	156	47.1	74	69.1	45	34.8	37	36.4
		Received rota 1 but penta 2 administered after 223 days of age	9	2.7	2	4.3	4	3.7	3	4.0

Table 5. Odds ratios of received rotavirus vaccine by pentavalent timing and birth cohort among children born 2007-2009 who received a dose of pentavalent vaccine. El Salvador, 2011

	Rotavirus Dose 1	
	Crude	**Adjusted[1]**
Pentavalent 1 prior to 104 days	1.0 (reference)	1.0 (reference)
Pentavalent 1 after 104 days	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)
Born in 2007	1.0 (reference)	1.0 (reference)
Born in 2008	1.9 (1.3, 2.8)	1.5 (1.0, 2.3)
Born in 2009	2.2 (1.5, 3.2)	2.2 (1.4, 3.6)
	Rotavirus Dose 2	
	Crude	**Adjusted[2]**
Pentavalent 2 prior to 223 days	1.0 (reference)	1.0 (reference)
Pentavalent 2 after 223 days	0.1 (0.1, 0.2)	0.6 (0.2, 1.7)
Born in 2007	1.0 (reference)	1.0 (reference)
Born in 2008	0.9 (0.7, 1.2)	0.3 (0.2, 0.5)
Born in 2009	1.1 (0.8, 1.4)	0.5 (0.3, 0.9)

[1]Adjusted for pentavalent dose 1 categorical timeliness, maternal education and birth cohort

[2]Adjusted for pentavalent dose 2 categorical timeliness, birth cohort, maternal education, and rotavirus dose 1 categorical

Table 6. Hazard ratios of received rotavirus vaccine by pentavalent timing and birth cohort among children born 2007-2009 who received a dose of pentavalent vaccine. El Salvador, 2011

	Rotavirus Dose 1[1]
Pentavalent 1 prior to 104 days	1.0 (reference)
Pentavalent 1 after 104 days	1.2 (1.1, 1.3)
	Rotavirus Dose 2[2]
Pentavalent 2 prior to 223 days	1.0 (reference)
Pentavalent 2 after 223 days	1.1 (0.9, 1.2)

[1]Adjusted for birth cohort

[2]Adjusted for birth cohort, maternal education, and rotavirus dose 1 categorical timeliness

Table 7. Hypothetical rotavirus vaccine coverage without upper age limits and without stock problems. El Salvador, 2011

		Year of Birth					
		2007 (n=806)		2008 (n=877)		2009 (n=812)	
		n	%	n	%	n	%
Rotavirus 1	Observed administered	732		832		775	
	Observed plus pentavalent 1 administered after 104 days of age	746	92.6%	838	95.6%	787	96.9%
	Observed plus reported lack of vaccine as reason for non-vaccination	780	96.8%	865	98.6%	807	99.4%
Rotavirus 2	Observed administered	700		754		709	
	Observed plus pentavalent 2 administered after 223 days of age and penta 1 administered after 104 days of age	762	94.5%	797	90.9%	739	91.0%
	Observed plus reported lack of vaccine as reason for non-vaccination	772	95.8%	852	97.1%	790	97.3%

Table 8. Concurrent administration of rotavirus and pentavalent vaccines among children born in 2007-2009. El Salvador, 2011.

		Total		Year of Birth					
				2007		2008		2009	
		n	% (CI)	n	% (CI)	n	% (CI)	n	% (CI)
Rotavirus Dose 1	Did not receive rota 1	156	6.4 (4.9, 7.8)	74	9.4 (6.9, 11.8)	45	5.2 (3.2, 7.1)	37	4.7 (3.0, 6.3)
	Received rota and penta 1 together	1,814	72.3 (69.9, 74.6)	592	73.0 (69.6, 76.5)	701	80.1 (77.0, 83.1)	521	63.2 (58.9, 67.5)
	Received rota and penta 2 together	167	6.9 (5.8, 8.1)	50	6.5 (4.6, 8.3)	34	3.9 (2.5, 5.4)	83	10.6 (8.2, 13.0)
	Did not receive rota 1 with the 1st or 2nd dose of penta	358	14.4 (12.8, 16.1)	90	11.1 (8.6, 13.7)	97	10.9 (8.7, 13.0)	171	21.5 (18.1, 24.8)
Rotavirus Dose 2	Did not receive rota 2	331	13.8 (11.7, 15.9)	106	13.6 (10.6, 16.5)	123	14.8 (11.6, 18.0)	102	12.9 (10.0, 15.7)
	Received rota and penta 2 together	1,613	64.5 (61.9, 67.0)	542	67.4 (63.6, 71.2)	610	68.9 (65.1, 72.7)	461	56.9 (53.0, 60.8)
	Received rota and penta 3 together	95	4.1 (3.2, 5.1)	20	2.5 (1.4, 3.7)	19	2.1 (1.1, 3.1)	56	7.9 (5.4, 10.4)
	Did not receive rota 2 with the 2nd or 3rd dose of penta	456	17.6 (16.1, 19.2)	138	16.5 (13.8, 19.3)	125	14.2 (11.5, 16.9)	193	22.4 (19.2, 25.5)

Table 9. Odds ratios of co-administration with another dose of pentavalent and odds of rotavirus vaccine solo administration as compared to rotavirus and pentavalent vaccine scheduled dose co-administration by birth cohort. El Salvador, 2011

Rotavirus Dose 1		**Crude**		**Adjusted[1]**	
		Rota1/Penta2	Rota1 alone	Rota1/Penta2	Rota1 alone
Year of Birth	2007	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
	2008	0.6 (0.3, 0.9)	0.9 (0.7, 1.2)	0.5 (0.3, 0.9)	0.9 (0.6, 1.2)
	2009	1.9 (1.3, 2.7)	2.2 (1.6, 3.0)	1.8 (1.2, 2.7)	2.0 (1.5, 2.8)
Rotavirus Dose 2		**Crude**		**Adjusted[2]**	
		Rota2/Penta3	Rota2 alone	Rota2/Penta3	Rota2 alone
Year of Birth	2007	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
	2008	0.8 (0.4, 1.6)	0.8 (0.6, 1.1)	1.5 (0.7, 3.5)	0.9 (0.6, 1.4)
	2009	3.7 (2.1, 6.6)	1.6 (1.2, 2.1)	3.6 (1.9, 6.9)	1.3 (0.9, 1.8)

[1]Adjusted for urban residence, maternal education, maternal employment status, and number of residents in the household

[2]Adjusted for urban residence, maternal education, maternal employment status, number of residents in the household, and co-administration of rotavirus vaccine dose 1

FIGURES

Figure 1. Cumulative incidence curve showing probability of vaccination with rotavirus vaccine doses 1 and 2 by the timing of the corresponding dose of pentavalent vaccine. El Salvador, 2011

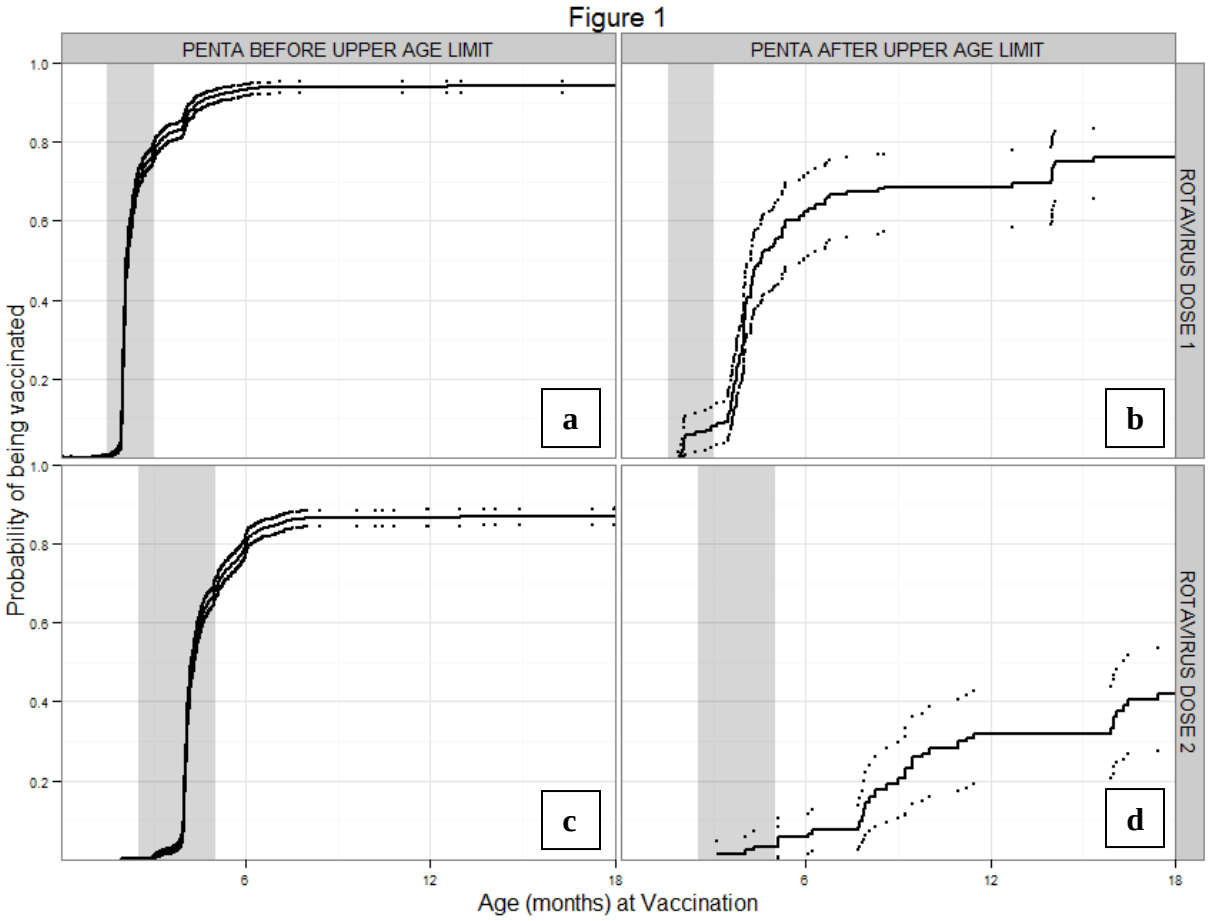


Figure 2. Cumulative incidence curve showing probability of vaccination with pentavalent vaccine doses 1 and 2 by birth cohort. El Salvador, 2011

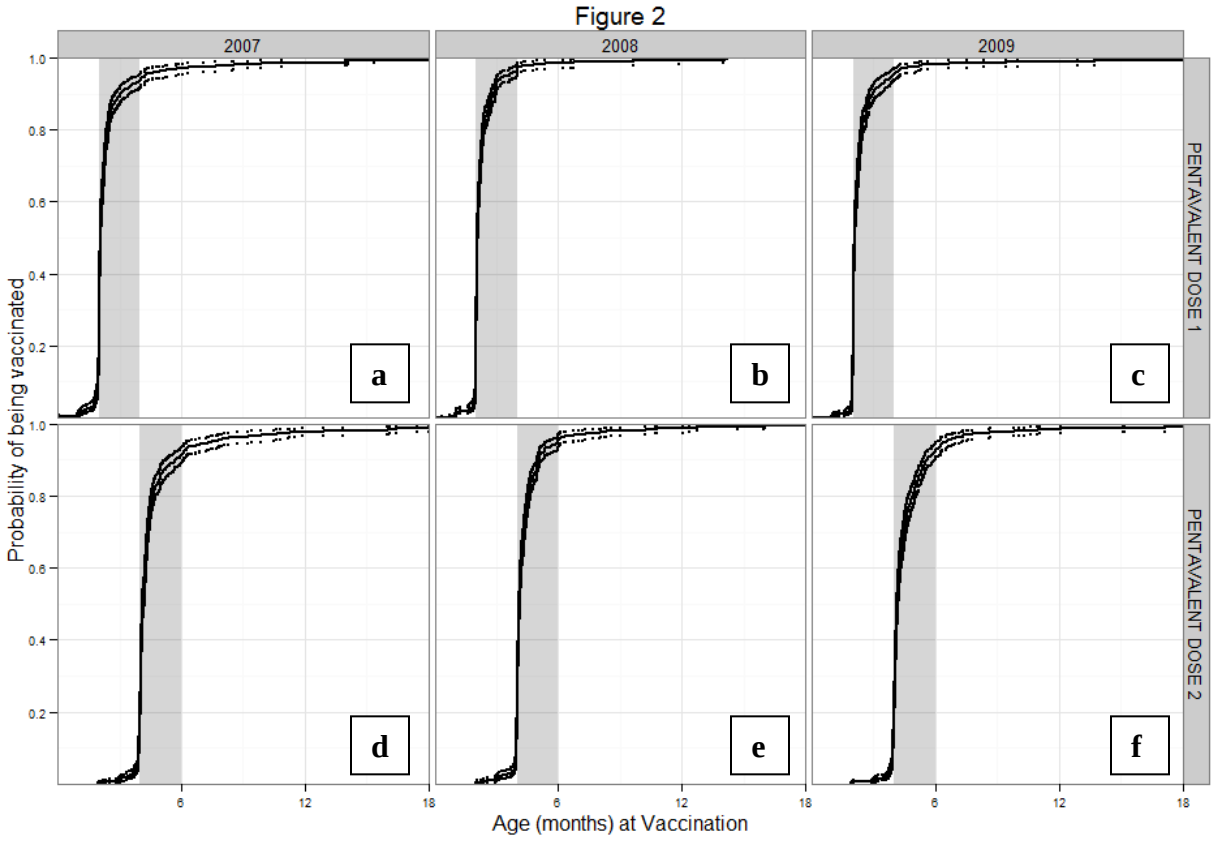


Figure 3. Cumulative incidence curve showing probability of vaccination with rotavirus vaccine doses 1 and 2 by birth cohort. El Salvador, 2011

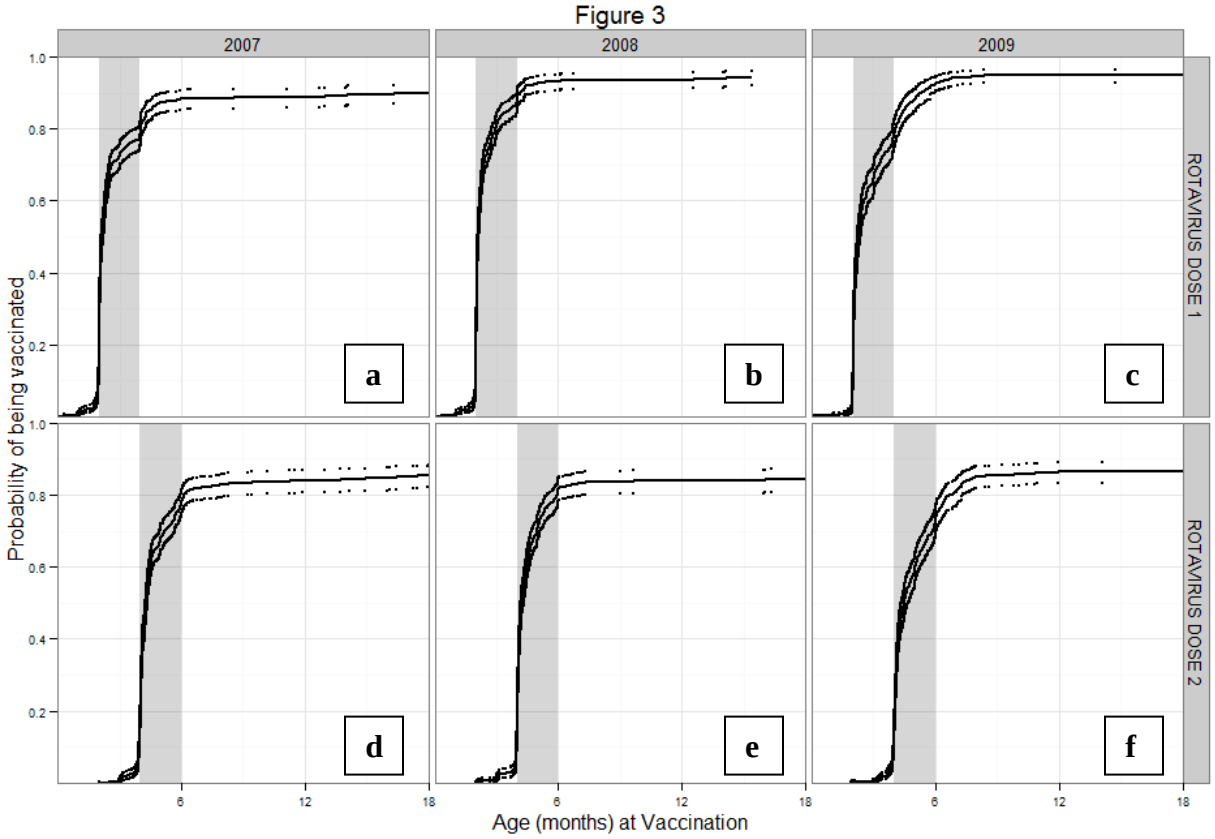


Figure 4. Number of first rotavirus vaccine doses administered by month. El Salvador, 2011

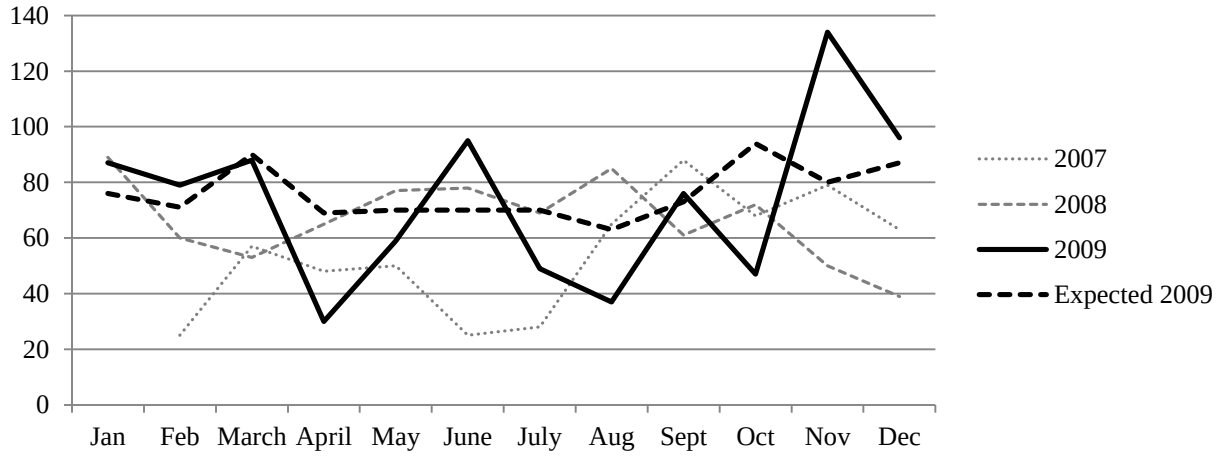
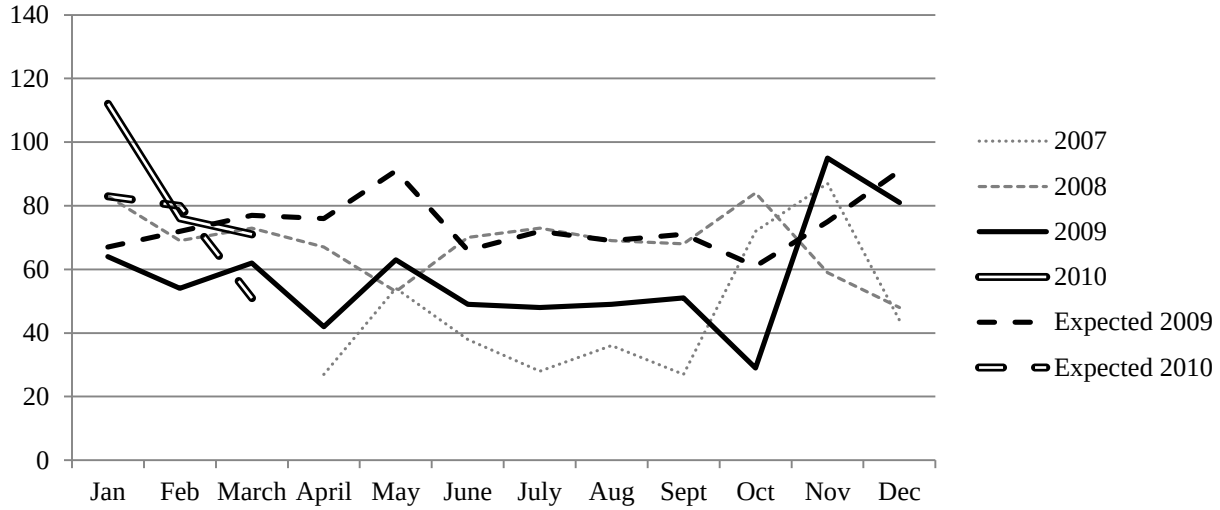


Figure 5. Number of second rotavirus doses administered by month.
El Salvador, 2011



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APPENDIX: MODELS AND MODELING STRATEGY

Fourteen different models were fit in this study. Models 1-4 and 10-14 were binary logistic models for predicting administration of first or second rotavirus doses. Models 7-9 were polytomous (i.e. multinomial) regression models for predicting 3 categories of co-administration of rotavirus and pentavalent doses. Models 5-6 were Cox regression models for time until administration of first (Model 5) or second (Model 6) rotavirus dose. Models 2, 4, 6, 9, 10, 11, and 14 adjusted for possible confounding. Confounding was assessed using the backwards elimination a change-in-estimate approach described by Kleinbaum and Klein (2010).

Model 1: Crude Binary Logistic Regression Model for First Rotavirus Vaccine Dose

$\text{Logit } P(X) = \alpha + \beta_1 * E_1$

Binary outcome status = administration of the first dose of rotavirus vaccine

Where 1= administered

0= not administered

E_1 = 1 if first dose of pentavalent vaccine administered after 104 days of age;

=0 if first dose of pentavalent vaccine administered on or before 104 days of age

Model 2: Binary Logistic Regression Model for First Rotavirus Vaccine Dose Adjusted for Maternal Education and Birth Cohort

$\text{Logit } P(X) = \alpha + \beta_1 * E_1 + \gamma_1 * C_1 + \gamma_2 * C_{21} + \gamma_3 * C_{22}$

Binary outcome status = administration of the first dose of rotavirus vaccine

Where 1= administered

0= not administered

E_1 = 1 if first dose of pentavalent vaccine administered after 104 days of age;

=0 if first dose of pentavalent vaccine administered on or before 104 days of age

C_1 = maternal education

Where 1= greater than 6^{th} grade

0= less than or equal to 6^{th} grade

C_{21}= 1 if 2008 birth cohort; else = 0

C_{22}= 1 if 2009 birth cohort; else = 0

[Reference group for C_{21} and C_{22}: 2007 birth cohort]

Model 3: Crude Binary Logistic Regression Model for Second Rotavirus Vaccine Dose

$\text{Logit } P(X) = \alpha + \beta_1 * E_3$

Bbinary outcome status = administration of the second dose of rotavirus vaccine

Where 1= administered

0= not administered

E_3 = 1 if first dose of pentavalent vaccine administered after 223 days of age;

=0 if first dose of pentavalent vaccine administered on or before 223 days of age

Model 4: Binary Logistic Regression Model for Second Rotavirus Vaccine Dose Adjusted for Maternal Education, Birth Cohort, and First Rotavirus Vaccine Dose Timing

$\text{Logit } P(X) = \alpha + \beta_1 * E_3 + \gamma_1 * C_1 + \gamma_2 * C_{21} + \gamma_3 * C_{22} + \gamma_4 * C_3$

Binary outcome status = administration of the second dose of rotavirus vaccine

Where 1= administered

0= not administered

E_3 = 1 if first dose of pentavalent vaccine administered after 223 days of age;

=0 if first dose of pentavalent vaccine administered on or before 223 days of age

C_1= maternal education

Where 1= greater than 6th grade

0= less than or equal to 6th grade

C_{21}= 2008 birth cohort

C_{22}= 2009 birth cohort

[Reference group for C_{21} and C_{22}: 2007 birth cohort]

C_3 = 1 if first dose of pentavalent vaccine administered after 104 days of age;

=0 if first dose of pentavalent vaccine administered on or before 104 days of age

Model 5: Stratified (on birth cohort) Cox Regression Model for Time Until First Rotavirus Vaccine Dose

$h_g(t, X) = h_{0g}(t)e^{\beta_1 * E_1}$

Where g= 1 (birth year 2007), g= 2 (birth year 2008, g= 3 (birth year 2009)

Outcome variable = time until administration of the first dose of rotavirus vaccine

Censoring status: 1 if first rotavirus dose administered

vs. 0 if first rotavirus dose not administered

E_1 = 1 if first dose of pentavalent vaccine administered after 104 days of age;

=0 if first dose of pentavalent vaccine administered on or before 104 days of age

Model 6: Stratified (on birth cohort) Cox Regression Model for Time Until Second Rotavirus Vaccine Dose Adjusted of Timing of First Rotavirus Vaccine Dose

$h_g(t, X) = h_{0g}(t)e^{\beta_1 * E_3 + \gamma_1 * C_1}$

Where g= 1 (birth year 2007), g= 2 (birth year 2008, g= 3 (birth year 2009)

Outcome variable = time until administration of the second dose of rotavirus vaccine

Censoring status: 1 if second rotavirus dose administered

vs. 0 if second rotavirus dose not administered

E_3 = 1 if first dose of pentavalent vaccine administered after 223 days of age;

=0 if first dose of pentavalent vaccine administered on or before 223 days of age

C_1 = 1 if first dose of rotavirus vaccine administered after 104 days of age;

=0 if first dose of rotavirus vaccine administered on or before 104 days of age

Model 7: Polytomous Logistic Regression Model 1 for Co-Administration of First Rotavirus Vaccine Dose and Pentavalent Vaccine Doses 1 and/or 2

Logit $P_g(X) = \alpha_g + \beta_{g1}*E_{11} + \beta_{g2}*E_{12}$

Where g= 1 (rotavirus vaccine dose 1 not administered)

g= 2 (co-administered with penvalent vaccine dose 2)

g= 3 (not co-administered with pentavalent vaccine doses 1 or 2)

[Reference group: rotavirus dose 1 and pentavalent dose 1 co-administered]

[Note: it is not possible to receive the first dose of rotavirus vaccine and the first and second doses of rotavirus vaccine on the same date.]

E_{11}= 1 if 2008 birth cohort; else = 0

E_{12}= 1 if 2009 birth cohort; else = 0

[Reference group for E_{21} and E_{22}: 2007 birth cohort]

Model 8: Polytomous Logistic Regression Model 2 for Co-Administration of Second Rotavirus Vaccine Dose and Pentavalent Vaccine Doses 2 and/or 3

Logit $P_g(X) = \alpha_g + \beta_{g1}*E_{11} + \beta_{g2}*E_{12}$

Where g= 1 (rotavirus vaccine dose 2 not administered)

g= 2 (co-administered with penvalent vaccine dose 3)

g= 3 (not co-administered with pentavalent vaccine doses 2 or 3)

[Reference group: rotavirus dose 2 and pentavalent dose 2 co-administered]

E_{11}= 1 if 2008 birth cohort; else = 0

E_{12}= 1 if 2009 birth cohort; else = 0

[Reference group for E_{21} and E_{22}: 2007 birth cohort]

Model 9: Adjusted Polytomous Logistic Regression Model 2 for Co-Administration of Second Rotavirus Vaccine Dose and Pentavalent Vaccine Doses 2 and/or 3

$$\text{Logit } P_g(X) = \alpha_g + \beta_{g1}*E_{11} + \beta_{g2}*E_{12} + \gamma*C_{g1} + \gamma*C_{g2} + \gamma*C_{g3} + \gamma*C_{g4} + \gamma*C_{g51} + \gamma*C_{g52} + \gamma*C_{g53}$$

Where g= 1 (rotavirus vaccine dose 2 not administered)

g= 2 (co-administered with penvalent vaccine dose 3)

g= 3 (not co-administered with pentavalent vaccine doses 2 or 3)

[Reference group: rotavirus dose 2 and pentavalent dose 2 co-administered]

[Note: it is not possible to receive the second dose of rotavirus vaccine and the second and third doses of rotavirus vaccine on the same date.]

E_{11}= 1 if 2008 birth cohort; else = 0

E_{12}= 1 if 2009 birth cohort; else = 0

[Reference group for E_{21} and E_{22}: 2007 birth cohort]

C_1= maternal education

Where 1= greater than 6^{th} grade

0= less than or equal to 6^{th} grade

C_{g2}= urban residence

Where 1= urban residence

0= rural residence

C_{g3}= maternal employment status

Where 1= Employed outside the home

0= Not employed outside the home

C_{g4}= number of residents in the household

Where 1= less than or equal to 5 residents

0= greater than or equal to 6 residents

C_{g51}= 1 if rotavirus vaccine dose 1 co-administered with penvalent vaccine dose 2; else = 0

C_{g52}= 1 if rotavirus vaccine dose 1 not co-administered with pentavalent vaccine doses 1 or 2; else = 0

C_{g53}= 1 if rotavirus vaccine dose 1 not administered; else = 0

[Reference group for C_{g51}, C_{g52}, and C_{g53}: rotavirus dose 1 and pentavalent dose 1 co-administered]

[Note: it is not possible to receive the first dose of rotavirus vaccine and the first and second doses of rotavirus vaccine on the same date.]

<u>Model 10: Binary Logistic Model for Timeliness of First Pentavalent Vaccine Dose Adjusted for Maternal Education</u>

Logit P (X) = $\alpha + \beta_1 * E_{21} + \beta_1 * E_{22} + \gamma_1 * C_1$

Outcome= timely administration of the first dose of pentavalent vaccine

Where 1= timely administration (from 42- 90 days of age)

0= administered outside of timely period

E_{21}= 1 if 2008 birth cohort; else = 0

E_{22}= 1 if 2009 birth cohort; else = 0

[Reference group for E_{21} and E_{22}: 2007 birth cohort]

C_1 = maternal education

Where 1= greater than 6^{th} grade

0= less than or equal to 6^{th} grade

Model 11: Binary Logistic Model for Timeliness of Second Pentavalent Vaccine Dose Adjusted for Maternal Education and Timeliness of First Pentavalent Vaccine Dose

Logit P (X) = $\alpha + \beta_1 * E_{21} + \beta_1 * E_{22} + \gamma_1 * C_1 + \gamma_2 * C_{21} + \gamma_3 * C_{22} + \gamma_4 * C_{23}$

Outcome = timely administration of the second dose of pentavalent vaccine

Where 1= timely administration (from 70-120 days of age)

0= administered outside of timely period

E_{21}= 1 if 2008 birth cohort; else = 0

E_{22}= 1 if 2009 birth cohort; else = 0

[Reference group for E_{21} and E_{22}: 2007 birth cohort]

C_1= maternal education

Where 1= greater than 6^{th} grade

0= less than or equal to 6^{th} grade

C_{21}= 1 if the first dose of pentavalent vaccine administered before 42 days of age; else =0

C_{22}= 1 if the first dose of pentavalent vaccine administered from 91-104 days of age; else = 0

C_{23}= 1 if the first dose of pentavalent vaccine administered after 104 days of age; else = 0

[Referent group for C_{11} and C_{12}: first dose of pentavalent vaccine administered between 42 and 90 days of age]

Model 12: Crude Binary Logistic Model for Administration of First Rotavirus Vaccine Dose By Birth Cohort

Logit P (X) = $\alpha + \beta_1 * E_{21} + \beta_1 * E_{22}$

Outcome = administration of the first dose of rotavirus vaccine

Where 1= administered

0= not administered

E_{21}= 1 if 2008 birth cohort; else = 0

E_{22}= 1 if 2009 birth cohort; else = 0

[Reference group for E_{21} and E_{22}: 2007 birth cohort]

Model 13: Binary Logistic Model for Administration of Second Rotavirus Vaccine Dose By Birth Cohort

$\text{Logit } P(X) = \alpha + \beta_1 * E_{21} + \beta_1 * E_{22}$

Outcome= administration of the second dose of rotavirus vaccine

Where 1= administered

0= not administered

E_{21}= 1 if 2008 birth cohort; else = 0

E_{22}= 1 if 2009 birth cohort; else = 0

[Reference group for E_{21} and E_{22}: 2007 birth cohort]

Model 14: Binary Logistic Model for Administration of Second Rotavirus Vaccine Dose By Birth Cohort Adjusted for Maternal Education and Timeliness of Second Pentavalent Vaccine and First Rotavirus Vaccine Doses

$\text{Logit } P(X) = \alpha + \beta_1 * E_{21} + \beta_2 * E_{22} + \gamma_1 * C_1 + \gamma_2 * C_{21} + \gamma_3 * C_{22} + \gamma_4 * C_{31} + \gamma_5 * C_{32}$

Outcome= administration of the second dose of rotavirus vaccine

Where 1= administered

0= not administered

E_{21}= 2008 birth cohort

E_{22}= 2009 birth cohort

[Reference group for C_{21} and C_{22}: 2007 birth cohort]

C_1= maternal education

Where 1= greater than 6^{th} grade

0= less than or equal to 6^{th} grade

C_{21} = 1 if the second dose of pentavalent vaccine administered before 70 days of age; else = 0

C_{22} = 1 if the second dose of pentavalent vaccine administered after 223 days of age; else = 0

[Referent group for E_{31} and E_{32}: second dose of pentavalent vaccine administered between 70 and 223 days of age]

C_{31}= 1 if the first dose of rotavirus vaccine administered before 42 days of age; else =0

C_{32}= 1 if the first dose of rotavirus vaccine administered after 104 days of age; else = 0

[Referent group for C_{31} and C_{32}: first dose of rotavirus vaccine administered between 42 and 104 days of age]