Changes in Childhood Diarrhea Incidence in Nicaragua Following 3 Years of Universal Infant Rotavirus Immunization

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Background: Although the pentavalent rotavirus vaccine was highly efficacious against rotavirus diarrhea in clinical trials, the effectiveness of vaccine under field conditions in the developing world is unclear. In October 2006, Nicaragua became the first developing nation to implement universal infant immunization with the pentavalent rotavirus vaccine. To assess the effect of the immunization program, we examined the incidence of diarrhea episodes between 2003 and 2009 among children in the state of León, Nicaragua.

Methods: We extracted data on diarrhea episodes from health ministry records. We used scaled Poisson regression models to estimate diarrhea incidence rate ratios for the period following the program's implementation to the period before implementation.

Results: Following implementation of the immunization program, diarrhea episodes among infants were reduced (incidence rate ratios: 0.85, 95% confidence interval: 0.71–1.02) during the rotavirus season, but appear to have increased during other months.

Conclusions: Although the immunization program appears effective in reducing diarrhea episodes during the rotavirus season, a large burden of diarrhea still persists during the remainder of the year.

Key Words: rotavirus, diarrhea, child, rotavirus vaccine, Nicaragua

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Diarrhea is among the leading infectious killers of children worldwide, second only to pneumonia in its contribution to child mortality. Rotavirus, the most important cause of diarrhea, is responsible for an estimated 527,000 deaths[1] and 138 million episodes of diarrhea[2] in the world each year. Although oral rehydration programs have been successful in reducing the mortality from diarrhea, the overall incidence of diarrhea has not declined since the 1950s.[3] The introduction of 2 rotavirus vaccines in 2006 offered new tools to prevent both diarrhea episodes and diarrhea-related deaths.

In Nicaragua, rotavirus had been detected in 28% of children who received care for diarrhea.[4] As found elsewhere in the developing world, Nicaraguan children historically acquired their first rotavirus infection at a young age; by 1 year, 90% had developed symptomatic rotavirus diarrhea or had evidence of seroconversion.[5] The highest peak of rotavirus transmission in Central America occurs during the dry season (Quarter 1, January to March).[6]

In October 2006, Nicaragua became the first nation eligible for funding by the GAVI Alliance to begin universal infant rotavirus immunization. Nicaraguan infants receive the pentavalent rotavirus vaccine (Rotateq, Merck) through the national expanded program on immunization at the ages of 2, 4, and 6 months. The rotavirus vaccine was made available to all infants who were born on or after August 2006. Children born before this time were not eligible to receive the vaccine. By the end of 2007, the local health ministry in León, Nicaragua, reported that the vaccine's coverage in the state was 98% for receipt of the first dose, 93% for receipt of the second dose, and 77% for receipt of all 3 doses. The coverage for the complete series in León's 10 municipalities ranged from 61% to 82%.

Although the pentavalent rotavirus vaccine was shown to prevent 98% of severe rotavirus gastroenteritis in clinical trials, these trials occurred primarily in Europe and the United States.[7] It is unclear whether the rotavirus vaccines will perform as well in the developing world, due to factors such as the distribution of rotavirus genotypes,[8–11] the simultaneous use of the oral polio vaccine,[12–14] a higher prevalence of malnutrition[15–17] and breastfeeding,[18–21] and possible inadequate vaccine storage conditions. The monovalent rotavirus vaccine provided only 49% efficacy against severe rotavirus gastroenteritis in a recent clinical trial in Malawi, significantly lower than the vaccine's efficacy in upper-income countries.[22,23] Similarly, a case-control study based in 4 Nicaraguan hospitals found the pentavalent rotavirus vaccine to be 58% effective against severe rotavirus diarrhea.[24]

To quantify the effect of the rotavirus immunization program in Nicaragua, we compared the incidence of all-cause diarrhea and diarrhea-related mortality in children before and after the immunization program using data collected by the local health ministry in the state of León, Sistemas Locales de Atención Integral a la Salud (SILAIS). By examining the effect for several years after the introduction of the immunization program, we reduced the effect of possible annual variation of rotavirus transmission.

METHODS

Setting

The state of León includes Nicaragua's second largest city, the municipality of León, and 9 rural municipalities. The state's

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total estimated population (2009) is 393,340 including 39,562 children under age 5. The climate is tropical with a dry season lasting from December to April.

Health Facilities and Information Management

The public health care system in León is organized into primary care (13 primary care centers and 93 health posts) and secondary care (referral hospital in León municipality). All primary care facilities provide outpatient care for diarrhea, primarily with oral rehydration solution; the 13 primary care centers are able to initiate intravenous hydration. Children requiring inpatient care are referred to the hospital. Beginning in 2008, León transitioned to sectorización, a model of health care where primary care providers are responsible for a geographic area. Providers visit families in the area at least annually, and visit young children more frequently.

All health facilities in Nicaragua are under a government mandate to report all visits for acute diarrhea episodes and deaths due to diarrhea to their local health ministry. Diarrhea was defined as ≥3 liquid or loose stools within a 24-hour period, with or without dehydration. Reports are made by "health statisticians" at the primary care centers and hospital and by nurses at the smaller health posts.

In León, the electronic reportable illnesses database is maintained at the SILAIS office, and includes information on the patient's age, gender, municipality, and date of the visit to the health facility. SILAIS estimates that 5% of diarrhea visits are not reported because of limited reporting from private clinics. On the basis of hospital records between 2008 and 2009, less than one-quarter of the total diarrhea visits among infants occurred in the hospital setting.

The national census in Nicaragua is conducted every 10 years by the Nicaraguan Institute of Development Information (INIDE), including 1995 and 2005. Official regional population estimates are made by SILAIS for the years between the census; these estimates incorporate yearly population reports obtained from each health sector, a unit of approximately 2000 individuals. According to these estimates, between 2005 and 2009, there was a 1% increase in the total population in the state of León and a 16% decrease in the size of the under 5-year-old population. The decrease in the childhood population size in León is attributed to the dramatic decline in the fertility rate among Nicaraguan women,[25] and the emigration of Nicaraguan families to neighboring countries in search of economic opportunities.[26]

Age categories in the census and reportable illnesses database include "under 12 months" and "12 to 59 months." Beginning in August 2007, all of the children in the "under 12 months" age category would have been eligible to receive the rotavirus vaccine. An increasing proportion of children in the "12 to 59 month" age category would have been eligible to receive the vaccine with increasing time since the vaccine's introduction.

Statistical Analyses

The primary outcome examined was the incidence rate of diarrhea episodes among infants in the pre- and postvaccine periods, because infants are the age group with the highest burden of rotavirus diarrhea, and because older children were not eligible to receive the vaccine when the program began. We first extracted and plotted the numbers of diarrhea episodes per week from SILAIS records between January 2003 and September 2009. We anticipated that vaccine effects would be greatest during the rotavirus season (Quarter 1, January to March) and defined quarters of interest (weeks: 1–13, 14–26, 27–39, and 40–52) before data analysis. We grouped the counts of diarrhea episodes by quarter for each year and municipality. The corresponding exposure time for the infants was estimated as the number of weeks for which records were available times the number of infants living in the municipality during the year, based on annual SILAIS population estimates.

We used scaled Poisson regression models to estimate incidence rates of diarrhea episodes and their corresponding 95% confidence intervals (CI) by quarter. Scaled Poisson regression analysis was also used to estimate the incidence rate ratio (IRR) and 95% CI among infants for the period following implementation to the period before implementation, controlling for municipality, and to examine possible interaction between vaccine period and quarter. We excluded records for the period of October 16, 2006 to August 15, 2007 in estimating the IRR, because the program was being rolled out during this time, and not all infants in the "under 12 months" age category had the opportunity to receive the vaccine. We planned to report estimates of the IRRs separately for each quarter if we observed a significant quarter by vaccine period effect at the alpha = 0.10 level. Secondarily, we used the same approach to estimate the IRR for children aged 12 to 59 months.

We also extracted the numbers of diarrhea-related deaths among children between January 2003 and December 2009. We calculated the rate of diarrhea-related deaths and corresponding 95% CIs for the prevaccine period (January 2003 to December 2006) and the postvaccine period (January 2007 through September 2009). Because of the anticipated small numbers of diarrhea-related deaths overall, we included all children under age 60 months in the calculation of rates.

RESULTS

Diarrhea Episodes

The numbers of diarrhea episodes by year and surveillance week for both infants and children are shown in Figure 1. In the period before the program's implementation (January 2003–October 2006) there were 10,313 diarrhea episodes reported for children under 12 months in the state of León within a total of 38,857 infant years of exposure. In the postvaccine period (August 2007–September 2009) there were 5280 diarrhea episodes reported in the same age group, with 17,734 total infant years of exposure. Using yearly population estimates for each year of the study, the incidence rates by quarter ranged from 15.9 to 31.9 diarrhea episodes per 100 infant years before the immunization program. In the period following program implementation, the incidence rates ranged from 18.7 to 37.5 diarrhea episodes per 100 infant years (Table 1). Incidence rates by quarter for each individual year are shown in Figure 2.

The IRRs for the periods after versus before the program's implementation (Table 1) varied significantly by quarter (P = 0.001). In Quarter 1, there was a reduction in the incidence rate that approached statistical significance (IRR = 0.85, 95% CI: 0.71–1.02). However, during Quarters 2 and 3, the incidence rates were higher in the period following UIRI implementation (Table 1).

Among the children aged 12 to 59 months, the incidence rates by quarter ranged from 6.2 to 11.7 diarrhea episodes per 100 child-years before the immunization program and 7.4 to 16.4 diarrhea episodes per 100 child-years after the program's implementation. During Quarter 1, the incidence rate was unchanged in the period after versus before the program's implementation (IRR = 1.10, 95% CI: 0.90–1.34). During the other quarters, the incidence rates were increased after implementation of the program (Quarter 2: IRR = 1.26, 95% CI: 1.06–1.51; Quarter 3: IRR = 1.59, 95% CI: 1.35–1.87; Quarter 4: 1.21, 95% CI: 0.94–1.55).

Because the SILAIS population estimates showed a considerable decrease in the childhood population during the years of the

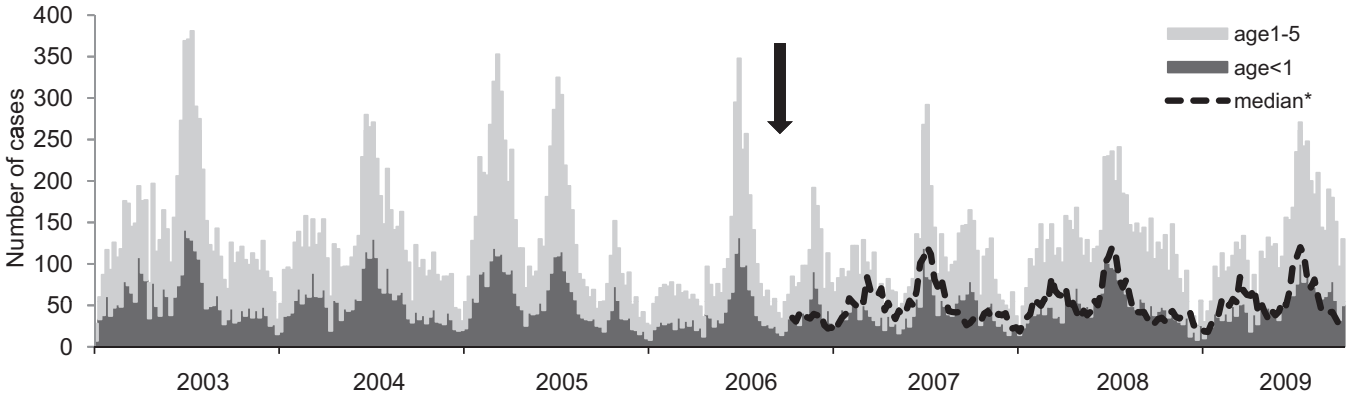

FIGURE 1. Numbers of diarrhea episodes by week, 2003 to 2009. Arrow indicates the start date for the rotavirus immunization program; *the median number of diarrhea episodes among infants by calendar week in the prevaccine period.

TABLE 1. Diarrhea Episodes in Infants in the Pre- and Postvaccine Periods*

Quarter	Episodes per 100 Infant Years (95% CI)		Incidence Rate Ratio (95% CI)
	Prevaccine	Postvaccine	
1	28.7 (24.6–33.4)	24.4 (19.5–30.5)	0.85 (0.71–1.02)
2	31.9 (26.9–37.8)	37.1 (32.7–42.0)	1.16 (1.00–1.35)
3	27.9 (22.2–35.1)	37.5 (33.3–42.2)	1.34 (1.16–1.55)
4	15.9 (13.7–18.3)	18.7 (16.0–21.9)	1.18 (0.95–1.47)

*Prevaccine, January 2003 to October 2006; Postvaccine, August 2007 to September 2009.

CI indicates confidence interval.

study, we performed a sensitivity analysis using the midpoint year population estimate (2006) for all study years. The IRRs among infants for the periods before versus following program implementation again varied significantly by quarter ($P = 0.001$). For Quarter 1, the reduction in the incidence rate among infants was greater (IRR = 0.69, 95% CI: 0.58–0.83) than in our primary analysis. During the other quarters, there were no changes in incidence rates among infants in the period following versus before the program's implementation (Table, Supplemental Digital Content 1, http://links.lww.com/INF/A605).

Diarrhea-related Mortality

Deaths from diarrhea for infants and children are shown in Table 2. There were no deaths among children aged 12 to 59 months in the years following the implementation of the immunization program. Overall, there were 1.03 diarrhea-related deaths per 10,000 child-years (95% CI: 0.64–1.57) in the years before the immunization program and 0.82 diarrhea-related deaths per 10,000 child-years (95% CI: 0.38–1.56) in the years following the immunization program's implementation.

DISCUSSION

In our primary analysis, we found a 15% decrease in all-cause diarrhea incidence among infants during the rotavirus seasons following the implementation of the immunization program. During the remainder of the year, we found an unexpected increase in the diarrhea incidence after implementation of the immunization program. Because population estimates showed a decrease in the childhood population over the years of the study, we performed a sensitivity analysis applying the 2006 population estimates for all years of the study. This analysis revealed a more dramatic decrease in diarrhea incidence of 31% during the rotavirus seasons following the immunization program, with no changes during the remainder of the year. These estimates correspond well to the rotavirus prevalence of 28% among Nicaraguan children with diarrhea before the immunization program,[4] and an analysis during the first rotavirus season after the immunization program was implemented, showing a 23% decrease in all-cause diarrhea episodes among infants.[27] As the majority of diarrhea visits occurred to primary care facilities, the moderate reduction may reflect the lower prevalence of rotavirus infection among milder cases of diarrhea as compared with more severe cases requiring a hospital visit.

Childhood deaths because of diarrhea trended downward in the years following the immunization program from a rate of 1.03 per 10,000 child-years to 0.82 per 10,000 child-years; however, because of the small numbers of deaths overall, we were unable to perform a rigorous analysis of the effect of the immunization program on diarrhea-related deaths. Interestingly, there were no reported diarrhea-related deaths among children ages 12 to 59 months in the years following implementation of the immunization program, despite the fact that a large proportion of children in this age category were not eligible to receive the vaccine when the program was implemented. This finding suggests either a direct effect of the vaccine among children over age 12 months in the second and third years of the immunization program or indirect effects of the vaccine in preventing rotavirus-related deaths among unimmunized children.

Although our results show a reduction in diarrhea incidence during the rotavirus seasons following the implementation of the immunization program, we did not anticipate a possible increase in diarrhea incidence during the remainder of the year. As we could not identify a biologically plausible explanation for an increase in diarrhea episodes, we believe that the changes in the postvaccine period may be because of an increase in reporting of diarrhea episodes. We identified several factors that may be contributing to a change in the reporting of diarrhea episodes during the postvaccine period as compared with the prevaccine period, which may bias against the benefit of the vaccine: (1) a health worker strike during late 2005 and early 2006 may have resulted in a decrease in reporting during these months in the prevaccine period, (2) increasing cell phone use in recent years has facilitated collection of epidemiological data, with less missing reports, (3) sectorización, or placing primary care providers in the community outside of

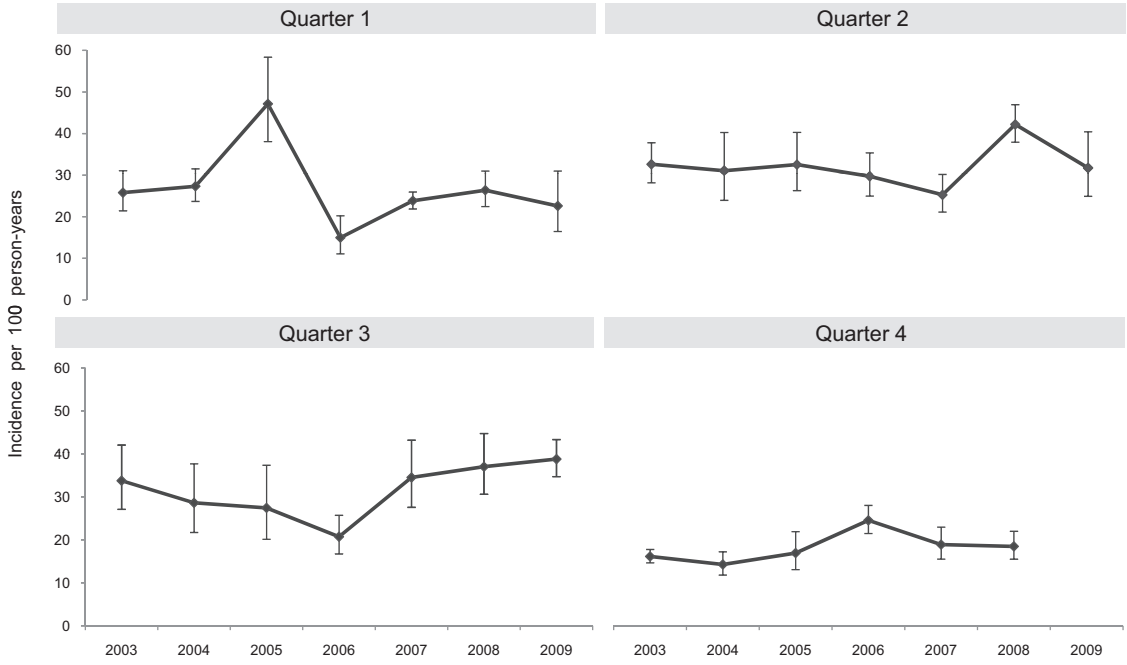

FIGURE 2. Incidence rates of diarrhea episodes in infants by quarter, 2003 to 2009.

TABLE 2. Deaths of Children From Diarrhea in León, Nicaragua, 2003 to 2009

	2003	2004	2005	2006	2007	2008	2009
Under 12 mo	3 (0)*	1 (0)	6 (5)	5 (2)	2 (1)†	5 (0)	4 (0)
12 to 59 mo	2 (0)	0 (0)	2 (1)	2 (1)	0 (0)	0 (0)	0 (0)
Total	5 (0)	1 (0)	8 (6)	7 (3)	2 (1)	5 (0)	4 (0)

*Deaths that occurred during the first quarter are shown in parentheses.
†Infant had not received the rotavirus vaccine.

health facilities beginning in 2008 may have increased reporting of diarrhea episodes through increased contact between the population and providers, and (4) the public awareness campaign during the vaccine's introduction in 2006 may have spurred more parents to bring their children to health providers for diarrhea, causing an increase in diarrhea visits. Establishing an active surveillance system for diarrhea episodes and diarrhea-related deaths in the years before the implementation of the immunization program and ensuring a consistent method of reporting during the years following the immunization program would have been one way to avoid possible changes in reporting. However, providing active surveillance at 107 health facilities over a 7-year period would have required overcoming multiple logistical challenges and great expense.

A potential limitation of the study is our definition of the rotavirus season as the first quarter of the year, based on regional seasonality data.[6] We acknowledge that the timing of the rotavirus season cannot be precisely determined from the available data and may vary from year to year.

In conclusion, in the years following the introduction of a universal rotavirus immunization program, there was a reduction in all-cause diarrhea incidence during the rotavirus seasons. The persistent burden of diarrhea during the remainder of the year draws attention to other diarrhea etiologies in the postvaccine period, such as *Shigella* spp, and enterotoxigenic *Escherichia coli*.[28] Hygiene, water, and sanitation programs[29] or the development of other enteric vaccines should be pursued in addition to rotavirus immunization programs to reduce childhood diarrhea year-round.

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