ORIGINAL ARTICLE

Effect of Rotavirus Vaccination on Death from Childhood Diarrhea in Mexico

Vesta Richardson, M.D., Joselito Hernandez-Pichardo, M.D., Manjari Quintanar-Solares, M.D., Marcelino Esparza-Aguilar, M.D., Brian Johnson, B.S., Cesar Misael Gomez-Altamirano, M.D., Umesh Parashar, M.D., M.P.H., and Manish Patel, M.D.

ABSTRACT

BACKGROUND

A phased introduction of a monovalent rotavirus vaccine occurred in Mexico from February 2006 through May 2007. We assessed the effect of vaccination on deaths from diarrhea in Mexican children in 2008 and 2009.

METHODS

We obtained data on deaths from diarrhea, regardless of cause, from January 2003 through May 2009 in Mexican children under 5 years of age. We compared diarrhea-related mortality in 2008 and during the 2008 and 2009 rotavirus seasons with the mortality at baseline (2003–2006), before the introduction of the rotavirus vaccine. Vaccine coverage was estimated from administrative data.

RESULTS

By December 2007, an estimated 74% of children who were 11 months of age or younger had received one dose of rotavirus vaccine. In 2008, there were 1118 diarrhea-related deaths among children younger than 5 years of age, a reduction of 675 from the annual median of 1793 deaths during the 2003–2006 period. Diarrhea-related mortality fell from an annual median of 18.1 deaths per 100,000 children at baseline to 11.8 per 100,000 children in 2008 (rate reduction, 35%; 95% confidence interval [CI], 29 to 39; P<0.001). Among infants who were 11 months of age or younger, diarrhea-related mortality fell from 61.5 deaths per 100,000 children at baseline to 36.0 per 100,000 children in 2008 (rate reduction, 41%; 95% CI, 36 to 47; P<0.001). As compared with baseline, diarrhea-related mortality was 29% lower for children between the ages of 12 and 23 months, few of whom were age-eligible for vaccination. Mortality among unvaccinated children between the ages of 24 and 59 months was not significantly reduced. The reduction in the number of diarrhea-related deaths persisted through two full rotavirus seasons (2008 and 2009).

CONCLUSIONS

After the introduction of a rotavirus vaccine, a significant decline in diarrhea-related deaths among Mexican children was observed, suggesting a potential benefit from rotavirus vaccination.

From the National Center for Child and Adolescent Health, Ministry of Health, Mexico City (V.R., J.H.-P., M.Q.-S., M.E.-A., C.M.G.-A.); and the National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta (B.J., U.P., M.P.). Address reprint requests to Dr. Patel at the Centers for Disease Control and Prevention, 1600 Clifton Rd., MS A-47, Atlanta, GA 30333, or at mpatel@cdc.gov.

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Despite the improved safety of food, water, and sanitation and the aggressive promotion of noninvasive interventions (e.g., oral rehydration therapy) and prevention strategies (e.g., increased breast-feeding), diarrhea remains the second leading infectious cause of childhood death worldwide, accounting for approximately 1.8 million annual deaths in children under 5 years of age.[1] Rotavirus is the single most important cause of severe childhood diarrhea globally and annually causes more than half a million deaths among children under 5 years of age.[2,3] In a large clinical trial conducted in Latin America, the monovalent human rotavirus vaccine Rotarix (GlaxoSmithKline Biologicals) showed a protective efficacy of 85% against severe rotavirus disease and of 42% against severe diarrhea from any cause.[4-7] On the basis of these encouraging data, several countries in the Americas began including a rotavirus vaccine in their routine childhood immunization program in 2006.[8,9]

In Mexico, substantial reductions in diarrhea-related deaths and complications occurred from 1990 to 2002 as a result of improved sanitation and safe water, the promotion of breast-feeding and oral rehydration, and supplementation with a megadose of vitamin A.[10-12] These measures have reduced the number of diarrhea-related deaths occurring in the spring and summer months that were attributable to bacterial pathogens, but deaths during the fall and winter months, when the prevalence of rotavirus is increased, have persisted.[10] Because of the persistent burden of diarrhea-related deaths and hospitalizations from rotavirus, in 2006, Mexico became one of the first countries worldwide to introduce the monovalent rotavirus vaccine in its national immunization program.

Because prelicensure trials did not assess the effect of rotavirus vaccination on mortality from diarrhea, the assessment of whether the use of these vaccines will prevent diarrhea-related death is a high public health priority.[13] In this study, we examined trends in diarrhea-related deaths among Mexican children before and after the introduction of rotavirus vaccination and correlated these trends with data on vaccine coverage.

METHODS

POPULATION

Mexico has an annual birth cohort of 1.9 million infants. In Mexico, vaccines for children are obtained by one of three health care institutions: the Ministry of Health through the National Center for Child and Adolescent Health (CENSIA) purchases vaccine for 50% of Mexican infants; Instituto Mexicano del Seguro Social (IMSS) purchases vaccine for all workers and their families, constituting approximately 43% of the Mexican population; and Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE) purchases vaccine for all federal employees, representing approximately 7% of the population. In February 2006, the Ministry of Health introduced the monovalent rotavirus vaccine in impoverished regions of selected states in Mexico, accounting for less than 5% of the Mexican birth cohort. In November 2006, the vaccine was also made available for children who were insured through the IMSS, and in May 2007, the Ministry of Health extended the program to include all Mexican children born after February 1, 2007. It was recommended that infants receive two doses of vaccine, at 2 and 4 months of age.

VACCINE COVERAGE DATA

There were no surveys of rotavirus vaccine coverage during the years of our study. However, as the supplier of vaccine for half of Mexican infants, CENSIA maintains administrative coverage data for this population. Thus, we assessed vaccination coverage data available through CENSIA for this cohort of children. CENSIA, which purchases and distributes the vaccine to the states, uses an electronic registration system through which the Mexican states (territorial jurisdictions and health centers) report on the number of vaccine doses that have been administered (either one or two doses for the rotavirus vaccine). The recording and reporting of doses generally follow the recommendations of the World Health Organization (WHO).

At the local level, clinic workers maintain a tally sheet for the number of administered vaccine doses. A supervisor is responsible for checking the quality of the data at the local level. Each month, the clinics report to the state the number of doses that have been administered. State health workers subsequently transmit the aggregated data to CENSIA. We used the administrative method to assess rates of vaccine coverage.[14] The administrative method provides a crude estimate of coverage, which equals the annual number of doses administered, divided by the birth cohort that is eligible to receive vaccine purchased through CENSIA.

We calculated rotavirus vaccine coverage among children who were 11 months of age or younger and among those between the ages of 12 and 23 months at the end of 2007. A determination of vaccine coverage according to age at the end of 2007 allowed us to estimate the number of children who potentially would be protected from severe rotavirus disease during 2008.

DIARRHEA-RELATED DEATHS

For the period from January 2003 through May 2009, we obtained data on diarrhea-related deaths among Mexican children from the National Institute of Statistics, Geography, and Informatics and the Ministry of Health's General Directorate of Health Information, which collates all information from death certificates for children under 5 years of age. Data were accessed through the National System for Health Information.[15] From these data, we abstracted information on diarrhea-related deaths, using the following codes from the *International Classification of Diseases, 10th Revision*: A00–A03, A04, A05, A06.0–A06.3, A06.9, A07.0–A07.2, A07.9, and A08–A09.

EFFECT OF ROTAVIRUS VACCINE

We calculated the median rate of diarrhea-related death for each of the surveillance years, using population estimates for Mexico from the National Population Council for those years. We compared the rate of diarrhea-related death in 2008 with baseline data from 2003 through 2006. We also compared the absolute number of diarrhea-related deaths during the peak rotavirus-season months of December through May in 2008 and 2009 with the median number of deaths during the same months in baseline years. Because the rotavirus vaccine was introduced in 2006 and early 2007, we considered 2007 as a transitional year and excluded it from our analysis.

STATISTICAL ANALYSIS

We stratified our analysis according to age group: 0 to 11 months, 12 to 23 months, and 24 to 59 months. We calculated 95% confidence intervals for the reduction in the death rate. A two-sided P value of less than 0.05, as calculated with a chi-square test, was considered to indicate statistical significance. Analyses were performed with the use of SAS statistical software, version 9.2, and Microsoft Excel.

RESULTS

VACCINE COVERAGE

On the basis of CENSIA data, before the 2008 rotavirus season, 826,112 first doses and 565,797 second doses of monovalent rotavirus vaccine were administered in a target population that included 1.12 million infants who were 11 months of age or younger, for an overall vaccine coverage of 74% for the first dose and 51% for the second dose. Approximately 69,600 of the total doses (5%) were administered during 2006 in selected impoverished regions of 14 Mexican states. Because infants in these regions constitute less than 5% of the overall birth cohort in Mexico, it was unlikely that the vaccine program would have a major effect on the rate of diarrhea-related death nationwide. In addition, before the 2008 rotavirus season, CENSIA vaccine coverage was low among children between 12 and 23 months of age, with an estimated coverage of 4% for the first dose and 2% for the second dose in January 2008.

DIARRHEA-RELATED DEATHS

Of all diarrhea-related deaths in children under 5 years of age during the baseline years from 2003 through 2006, 67% occurred among infants who were 11 months of age or younger, 23% among those between 12 and 23 months of age, and 10% among those between 24 and 59 months of age. The rate of diarrhea-related death during the 2003–2006 period was markedly seasonal in both infants who were 11 months of age or younger and those between 12 and 23 months of age, with 65% of the deaths occurring from December through May (Fig. 1). In 2008, the seasonal peak in diarrhea-related deaths appeared to be substantially blunted among infants who were 11 months of age or younger but not among children between 12 and 23 months of age. In 2009, the reduction in deaths was sustained among infants 11 months of age or younger but was also evident among children between 12 and 23 months of age.

During the 2003–2006 period, an annual median of 1793 diarrhea-related deaths (range, 1464 to 2002) was reported in Mexico among children under 5 years of age, for a median annual rate of diarrhea-related death of 18.1 per 100,000 children; the median rates per 100,000 children were 19.6 in 2003, 17.7 in 2004, 18.7 in 2005,

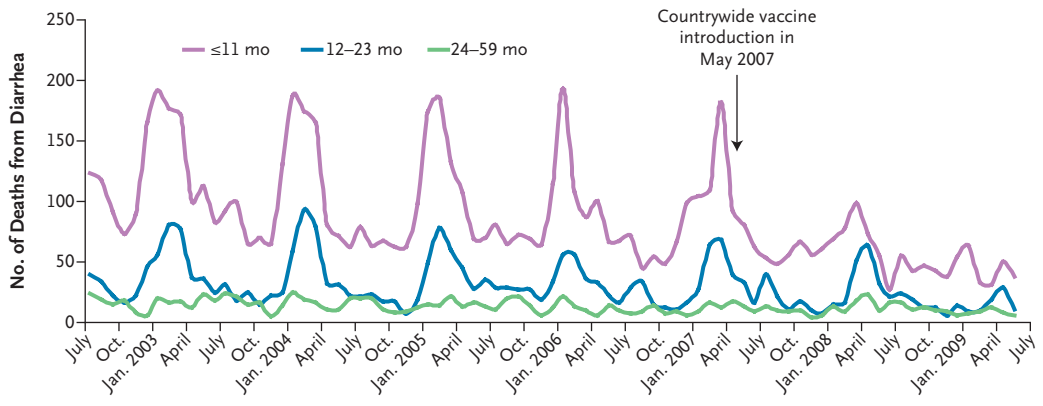

Figure 1. Number of Diarrhea-Related Deaths among Children 59 Months of Age or Younger from July 2002 through May 2009 in Mexico, According to Age Group.

and 15.1 in 2006. During 2008, the number of diarrhea-related deaths among children in this age group fell by 675 to a total of 1118, for a rate of death of 11.8 per 100,000 children, a relative reduction of 35% (95% confidence interval [CI], 29 to 39; P<0.001) (Table 1).

The decline in the rate of diarrhea-related death in 2008 was greatest among infants who were 11 months of age or younger, from a median of 61.5 per 100,000 children during the 2003–2006 period to 36.0 per 100,000 children in 2008, a relative reduction of 41% (95% CI, 36 to 47; P<0.001) (Table 1). In this age group, there were 680 deaths in 2008, as compared with 1197 during the baseline years, a reduction of 517 deaths. Among children between 12 and 23 months of age in 2008, there was also a significant decline in the number of diarrhea-related deaths, from 421 to 285 deaths, with a decrease in the rate per 100,000 children of 21.1 to 15.0, a relative reduction of 29% (95% CI, 17 to 39; P<0.001). In contrast, among children between 24 and 59 months of age, the decline in the number of diarrhea-related deaths, from 175 to 153, was not significant, with a relative rate reduction from 2.9 to 2.7, or 7% (95% CI, –14 to 26; P=0.44).

Among infants who were 11 months of age or younger, the peak in diarrhea-related deaths during the rotavirus-season months of December through May was substantially reduced in 2008 and 2009, as compared with both the median and the minimum number of deaths during these months in the 2003–2006 period (Fig. 2). During 2008, there was an absolute reduction of 517 deaths among infants 11 months of age or younger (Table 1). Of this reduction, 355 deaths (69%) were averted from December through May, from 789 deaths at baseline to 434 (Fig. 3); an additional 162 deaths (31%) were averted between June and November. The reduction persisted and was greater during the 2009 rotavirus season, when 520 fewer deaths occurred, a relative reduction of 66% as compared with baseline (Fig. 3).

Among children between 12 and 23 months of age, the peak in diarrhea-related deaths occurred 1 to 2 months later during the 2008 rotavirus season than during the baseline period but was substantially blunted during the 2009 rotavirus season (Fig. 2). As compared with the 290 diarrhea-related deaths in this age group during the baseline rotavirus season, the number of deaths during the rotavirus season was 184 in 2008 (a relative reduction of 37%) and 92 in 2009 (a relative reduction of 68%) (Fig. 3).

DISCUSSION

The recent addition of a monovalent rotavirus vaccine to Mexico's routine childhood immunization program may have contributed to a reduction in deaths related to diarrhea from any cause among Mexican children. These findings provide strong suggestive evidence of the beneficial effects of the vaccine against fatal illness from rotavirus. In the first two rotavirus seasons after the immunization program began, we noted a large reduction in the absolute number of deaths related to diarrhea from any cause, as compared with

Table 1. Changes in Diarrhea-Related Mortality among Children 59 Months of Age or Younger in 2008 in Mexico, as Compared with the Baseline Period (2003–2006), According to Age Group.*

Age Group	No. of Diarrhea-Related Deaths		Diarrhea-Related Rate of Death		Absolute Reduction		Relative Reduction in Rate of Death (95% CI)	P Value†
	Baseline (2003–2006)	2008	Baseline (2003–2006)	2008	No. of Deaths	Rate of Death		
			no. of deaths/100,000			*no. of deaths/100,000*	%	
All ages (0–59 mo)	1793	1118	18.1	11.8	675	6.3	35 (29 to 39)	<0.001
≤11 mo	1197	680	61.5	36.0	517	25.5	41 (36 to 47)	<0.001
12–23 mo	421	285	21.1	15.0	136	6.1	29 (17 to 39)	<0.001
24–59 mo	175	153	2.9	2.7	22	0.2	7 (–14 to 26)	0.44

* Baseline values are the sum of the monthly median numbers of diarrhea-related deaths during the 2003–2006 baseline period.
† P values were calculated with the use of a chi-square test.

the prevaccine baseline period. Approximately two thirds of this reduction in mortality occurred during the months of December through May, when 62 to 68% of laboratory-confirmed cases of rotavirus diarrhea requiring hospitalization are reported to occur in Mexico.[10] Given that a third of the cases of severe rotavirus disease in Mexico occur between June and November, our finding of a reduction during these months is not unexpected.

Although our ecologic analysis cannot provide definitive evidence that vaccination prevented deaths, the notable blunting of the typical seasonal peak in diarrhea-related deaths during two consecutive rotavirus seasons, especially among infants who were 11 months of age or younger and who received the greatest vaccine coverage, supports the premise that vaccination may have contributed to the reduction in diarrhea-related mortality. Moreover, because of the increasing number of older vaccinated children in 2009, the increased relative reduction in deaths among children between 12 and 23 months of age during the 2009 season (68%), as compared with the reduction of 37% in 2008, also supports a vaccine effect. Secular trends in declining mortality from diarrhea in Mexican children because of other factors (e.g., improvements in hygiene, sanitation, and access to care) also may have contributed to the decline, but the marked reduction in diarrhea-related deaths in 2008 and 2009, as compared with 2006, suggests that such environmental factors are unlikely to fully account for the decline. If the reduction in disease is sustained during future years, these data will provide an estimate of the vaccine-preventable burden of childhood diarrhea-related deaths attributable to rotavirus before the introduction of vaccine.

Our findings must be interpreted with some caveats. First, we did not have precise vaccine-coverage estimates for Mexico and could not quantify the reduction in the number of diarrhea-related deaths attributable to vaccination. Our vaccine-coverage estimates were based on data for children who were eligible to receive vaccine purchased by the Ministry of Health (through CENSIA) and did not reflect coverage estimates for all of Mexico. However, because CENSIA data account for approximately 50% of infants in Mexico, and because vaccine was made available to children who were insured through IMSS 6 months before it was available to those covered by CENSIA, these coverage estimates could underestimate nationwide coverage.

Second, secular variations in disease, including changes in coding practices, might also have affected the trends in diarrhea-related deaths. In addition, underreporting of diarrhea-related death is likely but would have been similar during the periods before and after the introduction of the vaccination program. The WHO estimates that approximately 3100 diarrhea-related deaths occur annually among children under the age of 5 years in Mexico,[2] and it is possible that many of these deaths occur outside the hospital, perhaps in impoverished areas where residents have limited access to health care. Access to vaccine and the effect of vaccination might differ between these areas and developed regions and thus warrant further assessment.

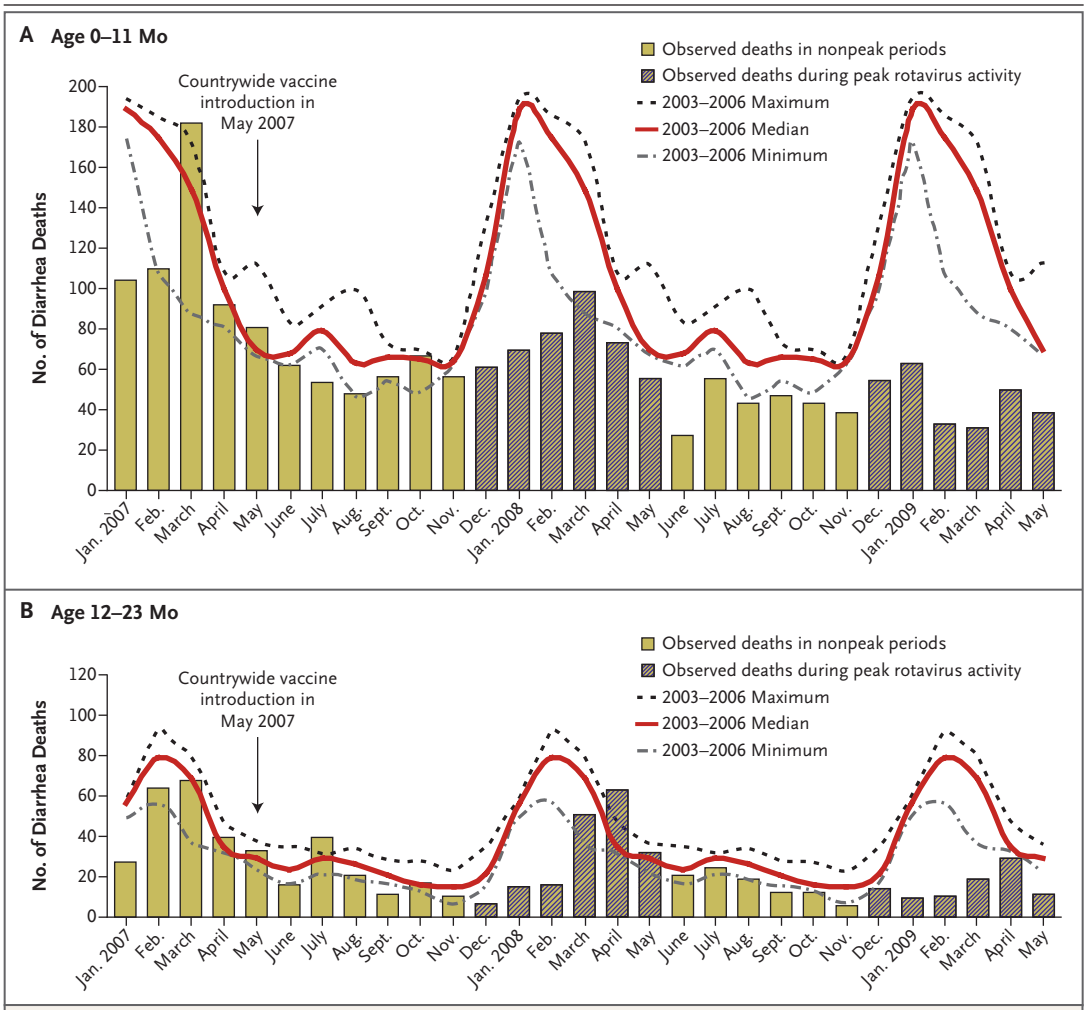

Figure 2. Number of Diarrhea-Related Deaths per Month among Children 23 Months of Age or Younger after the Introduction of Rotavirus Vaccination in Mexico, as Compared with the Baseline Period (2003–2006).

Third, because of challenges in obtaining fecal specimens to confirm the cause of diarrhea in children who died (especially since most deaths occurred outside medical facilities), we were unable to examine trends in deaths from rotavirus specifically. Nevertheless, the marked winter seasonality of rotavirus in Mexico[10] that was mimicked by the seasonal pattern of all diarrhea-related deaths allowed us to indirectly assess the effect of vaccination on the rate of death.

Finally, although case–control studies would provide a more specific measure of the effectiveness of vaccine in reducing mortality than ecologic assessments, such assessments are difficult, given the inherent diagnostic challenges in identifying rotavirus-related deaths.[16]

The significant reduction in diarrhea-related mortality among children between 12 and 23 months of age during 2008 was intriguing. Before 2008, vaccine coverage was less than 5% in this age group among children who were vaccinated through CENSIA. Although we did not have coverage data for IMSS, only 10 to 15% of the children between 12 and 23 months of age nationwide would have been age-eligible for rotavirus immunization before 2008. Thus, although vaccine uptake in these children might account for some reduction, the substantial decline of 29% in mortality from diarrhea from any cause in children between 12 and 23 months of age raises the possibility that vaccination may have reduced transmission of rotavirus disease in Mexico and

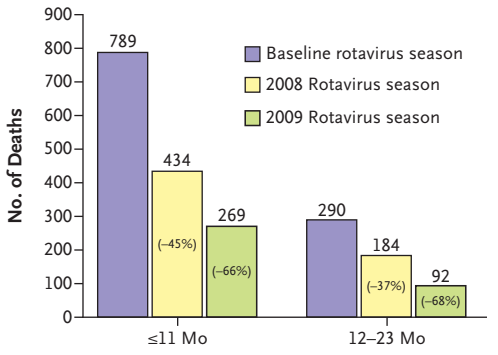

Figure 3. Number of Diarrhea-Related Deaths among Children 23 Months of Age or Younger during Rotavirus Seasons in 2008 and 2009, as Compared with the Baseline Period (2003–2006).

The median baseline value is the sum of the median numbers of diarrhea-related deaths during each of the rotavirus-season months of December through May for the 2003–2006 period for children who were 11 months of age or younger and those between 12 and 23 months of age. The numbers within the bars are the relative reductions in the observed numbers of deaths during 2008 and 2009, as compared with baseline.

induced herd protection. A recent analysis of severe nonfatal rotavirus disease in the United States also showed a decline that was substantially greater than expected on the basis of vaccination rates alone, including a reduction in disease among children who were not age-eligible for vaccination.[17,18] Besides direct benefits to vaccinated infants, it is possible that vaccination of a proportion of the population could reduce overall transmission of rotavirus in the community and thus also lead to a reduction in the rate of disease among unvaccinated children.

In summary, our findings indicate an encouraging reduction in diarrhea-related mortality among Mexican children during two consecutive rotavirus seasons after the addition of a rotavirus vaccine to the childhood immunization schedule. Ongoing monitoring of diarrhea-related deaths and epidemiologic case–control studies of vaccine effectiveness against hospitalization for such illness would be useful for confirming the association between a reduction in severe diarrhea-related events with vaccine introduction. Although cautious interpretation is required, the results of our assessment indicate that routinely collected data on mortality related to diarrhea from any cause could prove to be a useful source of monitoring of the effect of rotavirus vaccination.

No potential conflict of interest relevant to this article was reported.

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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