Uptake of Rotavirus Vaccine and National Trends of Acute Gastroenteritis among Children in Nicaragua

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Background. In October 2006, a new rotavirus vaccine was introduced in Nicaragua and was available free to all age-eligible children. We assessed vaccine uptake and trends in acute gastroenteritis (AGE) to assess vaccine impact.

Methods. We analyzed national data from the period 2001–2007 on the total number of AGE episodes and on RotaTeq vaccine dose administration during 2006–2007.

Results. After the introduction of RotaTeq, 1-dose vaccine coverage rates rapidly increased to 80% among age-eligible children. During the 2007 rotavirus season, when combined 2- and 3-dose vaccine coverage among children aged 0–11 months was ~26%, the total number of AGE episodes among children aged 0–11 months decreased by 23%, compared with a decrease of 6% among unvaccinated children aged 12–59 months. Furthermore, a 12% decrease in the number of all-cause hospitalizations for AGE was noted among children aged 0–11 months, whereas a ~5% increase was observed among children aged 12–59 months.

Conclusions. The high rate of vaccination among age-eligible children soon after vaccine introduction in Nicaragua indicates an efficient immunization program. However, in the age group at risk of rotavirus disease, vaccine coverage during the 2007 rotavirus season had yet to reach a level sufficient for making firm conclusions about vaccine impact. Epidemiologic studies to evaluate vaccine effectiveness and ongoing surveillance as vaccine uptake increases will allow a better assessment of vaccine impact.

Rotavirus is the most common cause of severe gastroenteritis in children <5 years of age worldwide, accounting for an estimated 2.4 million hospital admissions and 527,000 deaths each year [1, 2]. Because of the tremendous global burden of rotavirus, vaccine introduction has been a high priority for several international agencies, including the World Health Organization and the GAVI Alliance (formerly known as the Global Alliance for Vaccines and Immunizations) [3, 4]. Since 2006, 2 new rotavirus vaccines—RotaTeq (Merck) and Rotarix (GlaxoSmithKline)—have been licensed for use in many countries. Prelicensure clinical trials of each of these vaccines have demonstrated high efficacy against severe rotavirus disease (85%–98%) and all-cause AGE (42%–59%), as well as good safety profiles [5, 6].

As these vaccines are introduced in immunization programs, monitoring their impact will be a high priority. The key question is whether the performance of these vaccines during routine use in different settings will be similar to that in prelicensure trials [4, 7]. Previous experience with other rotavirus vaccines and with other oral vaccines (eg, polio vaccine) suggests that many factors, such as interference by maternal antibodies, breast-feeding, prevalent viral and bacterial gut infections, concomitant administration of oral polio vaccine, and malnutrition, might adversely affect the performance of these vaccines among children in low-income countries [8, 9]. In addition, the efficacy of these vaccines could vary in areas where the prevalence

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of strains is different from that in clinical trials. Thus, the pressing scientific and programmatic need during the postlicensure period will be to demonstrate the impact of the vaccine during routine use in heterogeneous settings.

Nicaragua represents a unique opportunity to investigate these issues for several reasons. First, at the end of October 2006, a new rotavirus vaccine, RotaTeq, was added to the national vaccination schedule. The decision to implement vaccination was driven, in part, by a large nationwide outbreak of rotavirus diarrhea in 2005 that led to an unexpected increase in diarrhea-associated mortality, hospitalizations, and outpatient visits and garnered substantial attention from decision makers and public health authorities in Nicaragua [10]. In 2006, the manufacturer provided the country with a 3-year supply of the vaccine, and Nicaragua became the first GAVI-eligible country to introduce rotavirus vaccine. Demonstration of vaccine uptake and potential impact on disease burden in this setting will guide future decisions regarding funding for rotavirus vaccination programs in Nicaragua and other GAVI-eligible countries. The goal of this study was to document the uptake of rotavirus vaccine after its introduction in the Nicaragua Expanded Program on Immunization (EPI). We also compared episodes of all-cause acute gastroenteritis (AGE) that required hospitalizations and clinic consultations in various age groups during the 2007 rotavirus season with episodes during the 5-year period before vaccine introduction.

METHODS

RotaTeq vaccine coverage. In Nicaragua, rotavirus vaccine is administered routinely through the EPI schedule at 2, 4, and 6 months of age with the combination vaccine (DTP5) against diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenza* type B. RotaTeq was introduced on 27 October 2006 and was made available for all children born after 27 August 2006. We were interested in (1) assessing the integration of RotaTeq in the EPI schedule and (2) correlating vaccine uptake with trends in AGE in the vaccinated age group. To assess the integration of the vaccine in the EPI schedule, we first assessed vaccination rates for RotaTeq in the vaccine-eligible group (ie, children who were age eligible to receive the vaccine or the monthly birth cohort beginning in September 2006) and compared it with coverage of the DTP5 vaccine in the same group.

Because RotaTeq was introduced in October 2006, children <6 months of age might have directly benefited from the vaccine during the 2007 rotavirus season (weeks 1–20). However, in Nicaragua, AGE-related events among children <5 years of age are tallied by age. Thus, we hypothesized that any potential vaccine impact would result in a reduction in the rate of disease from baseline among children <11 months of age without any similar reductions among children aged 12–59 months.

Vaccine coverage rates were determined using the administrative method [11, 12], by which vaccine coverage is equal to the number of administered doses (dose 1, 2, or 3) divided by the number of infants in the age group of interest (ie, vaccine eligible, 0–11 months of age, and 0–59 months of age). Our calculations assume that births in Nicaragua are uniformly distributed throughout the year.

Trends in AGE and vaccine impact. In Nicaragua, 85% of the population uses health care facilities operated by the Ministry of Health. Since January 2001, the Ministry has maintained computerized records on the total number of medically attended AGE-related events (outpatient visits and hospitalizations) and hospitalizations for AGE by week of year. The number of outpatient AGE-related events was estimated by subtracting the number of hospitalizations from the total number of AGE-related events. The available data are categorized in the following age groups: 0–11 months of age and 12–59 months of age. We compared the observed number of hospitalizations and consultations (ie, outpatient visits) since vaccine introduction with the expected number (ie, baseline) of events in each setting for each age category. The baseline value was calculated using the median number of visits during 2001–2005 to minimize the effect of year-to-year fluctuations in the rate of disease. Children 0–11 months of age may have benefited directly from the vaccine during the 2007 rotavirus season (weeks 1–20). In contrast, during this season, children 12–59 months of age remained unvaccinated. Thus, we hypothesized that, during the 2007 rotavirus season, the reduction in the total number of AGE-related events from baseline would be greater among children 0–11 months of age than among children 12–59 months of age.

To further assess secular trends, we calculated the annual change (increase or decrease) from baseline in the number of visits to a health care facility for AGE each year (2001–2005 and 2007). Because a 4-month nationwide strike among health care workers in Nicaragua precluded data collection in 2006, we excluded this year from our analysis.

RESULTS

RotaTeq vaccine coverage. In Nicaragua, coverage for dose 1 of DTP5 vaccine and the full series of DTP5 vaccine among children 0–59 months of age has been at a steady state of ~94% and ~85%, respectively, since 2001 [13]. Soon after vaccine introduction in October 2006, the first dose of RotaTeq was administered to ~80% of the children who were age eligible to receive the vaccine, closely mirroring the 96% coverage for the first dose of DTP5 vaccine that was observed during 2007 (Figure 1). The rapid vaccine uptake among the children who were age eligible to receive vaccine indicates an efficient immunization program in Nicaragua. On the basis of this uptake, RotaTeq vaccine coverage rates among children <5 years of age

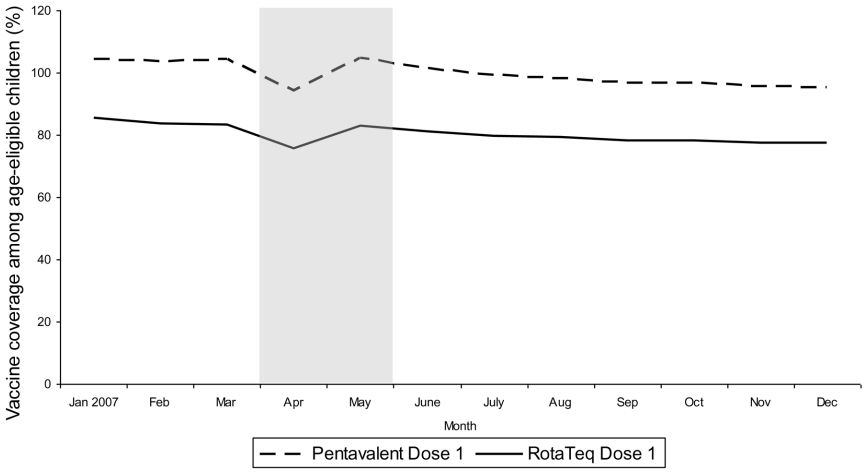

Figure 1. Comparison of coverage between RotaTeq vaccine and the first dose of combination vaccine with diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenza* type B (pentavalent DTP5) among age-eligible children in Nicaragua, January 2007-December 2007. Vaccine coverage was calculated by dividing the cumulative number of doses administered by the cumulative number of children born each month (assumed to be the yearly birth cohort divided by 12, or 12,476). Numbers exceed 100% in some months because of the assumption that the number of births per month is stable. The shaded area represents a period of belated reporting that resulted from a national vaccination day in April.

will approximate the currently steady-state DTP5 vaccine coverage rate of 85% by the end of 2012.

Because any anticipated vaccine impact would have occurred among children <1 year of age during the 2007 rotavirus season, we also assessed vaccination rates in this age group. Before week 1 of the 2007 rotavirus season (the season in Nicaragua typically coincides with the onset of rotavirus season in the rest of Central America), ~21% of children 0–11 months of age received at least 1 dose of RotaTeq. During the 2007 rotavirus season (weeks 1–20), a mean of 26% of children 0–11 months of age received ⩾2 doses of RotaTeq. By the end of the first year of the vaccine program (August 2007), 55,605 children

Table 1. Cumulative Number of Pentavalent and RotaTeq Doses Administered, by Month and Dose, in Nicaragua, October 2006–August 2007

	No. of pentavalent doses			No. of RotaTeq doses		
Year, month	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
2006						
November	13,866	11,031	11,173	12,536	1	…
December	24,674	20,027	19,808	21,045	833	…
2007						
January	39,050	33,832	31,460	32,700	10,417	128
February	51,696	45,291	41,629	42,426	18,418	1733
March	65,187	58,913	54,879	52,724	28,451	10,142
April[a]	70,564	64,627	60,504	57,253	33,141	14,479
May[a]	91,517	87,406	83,447	73,157	48,865	29,786
June	101,204	96,946	94,077	81,662	56,793	38,575
July	111,292	106,668	105,305	90,168	64,726	47,404
August	122,379	116,992	115,741	99,721	73,376	55,605
September	132,845	127,437	126,207	107,982	81,672	63,927
October	144,642	138,670	137,312	117,782	90,879	72,845
November	157,103	149,103	147,838	128,410	99,668	81,750
December	167,327	158,378	157,041	136,977	107,549	89,604

NOTE. The pentavalent vaccine (DTP5) is a combination vaccine against diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenza* type B. Data are from the Nicaraguan Ministry of Health [13].

[a] The nadir and peak values in April and May, respectively, represent belated reporting as a result of the annual national immunization day in April.

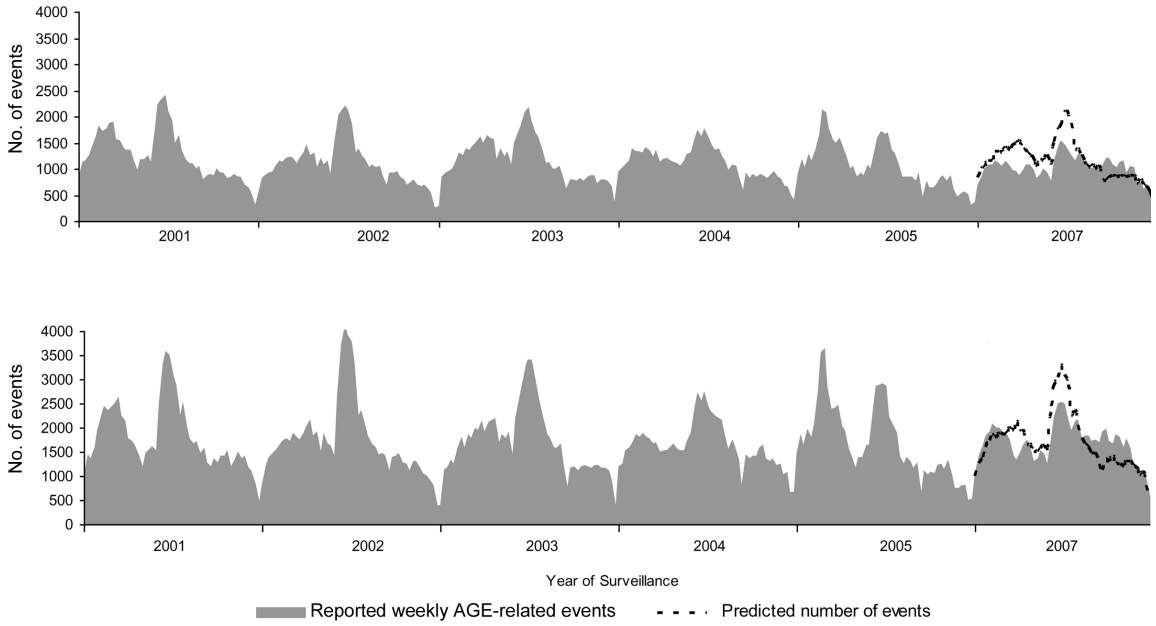

Figure 2. Total number of acute gastroenteritis (AGE)–related events among children aged 0–11 months *(top)* and children aged 12–59 months *(bottom),* by week and year, Nicaragua, 2001–2007. Data from 2006 were not used, because a nationwide health care worker strike prevented the accumulation of appropriate surveillance data for analysis. The predicted number of events represents the weekly median of total AGE-related events during 2001–2005. The median number of visits during weeks 1–20 in 2007 was 23% lower than predicted among children aged 0–11 months and 6% lower than predicted among children aged 12–59 months.

(37%) born after 1 September 2006 (ie, age eligible for vaccination) received 3 doses of RotaTeq vaccine (Table 1).

Trends in AGE and vaccine impact. We assessed trends in hospitalizations and consultations for AGE among the vaccinated children aged <1 year and among the unvaccinated children aged 1–5 years during the 2007 rotavirus season and compared these figures with those from the baseline years (2001–2005) (Figure 2). During the 2007 season, the observed number of weekly AGE-related events among children aged 0–11 months was consistently lower than the median number of episodes during the same weeks of the baseline years (Figure 3). When considering all medically attended AGE-related events, a reduction of ~23% was noted among children 0–11 months of age, compared with a reduction of ~6% among children aged 1–5 years. Among hospitalizations for AGE, there was an 11.7% decrease in the number of episodes of all-cause AGE among children aged 0–11 months during the 2007 rotavirus season, compared with a 4.7% increase among children aged 12–59 months (difference in proportions, 16.4%) (Figure 4). In contrast, when considering outpatient visits alone, the observed difference in the reduction in the number of cases of disease between the vaccinated and unvaccinated age groups was substantially lower, with a 27.6% reduction among children aged 0–11 months, compared with a 21.2% decrease among children aged 12–59 months (difference in proportions, 6.4%).

To demonstrate the contribution of secular trends, we also compared the median change (increase or decrease) from baseline during each year for the period 2001–2005. During each of these years, the increase or decrease from baseline in the number of hospitalizations for AGE was concordant for the 0–11-month and the 12–59-month age groups. In contrast, during 2007, a decrease of 11.7% in the number of hospitalizations for AGE was noted among the vaccinated children aged 0–11 months, whereas an increase of 4.6% was observed among the unvaccinated children aged 12–59 months (Figure 4).

DISCUSSION

Our data demonstrate the successful integration of a new rotavirus vaccine into the existing EPI schedule in Nicaragua, the first GAVI-eligible country to introduce rotavirus vaccine. Vaccine uptake increased rapidly after vaccine introduction, and the monthly administration of 1 vaccine dose to ~80% of children who are age eligible to receive vaccination indicates that logistical challenges of introducing a new vaccine in a low-income country can be overcome. The efficiency of the national vaccine program indicates that benefits in reducing the burden of AGE may soon be realized if the vaccine is as effective in the field setting as in the clinical trial. In the first rotavirus season after vaccine introduction, we observed a greater reduction (23%) in all-cause AGE-related events from baseline among the vaccinated children 0–11 months of age than among the unvaccinated children aged 12–59 months (~6% reduction). When focusing only on severe disease in 2007, a 12%

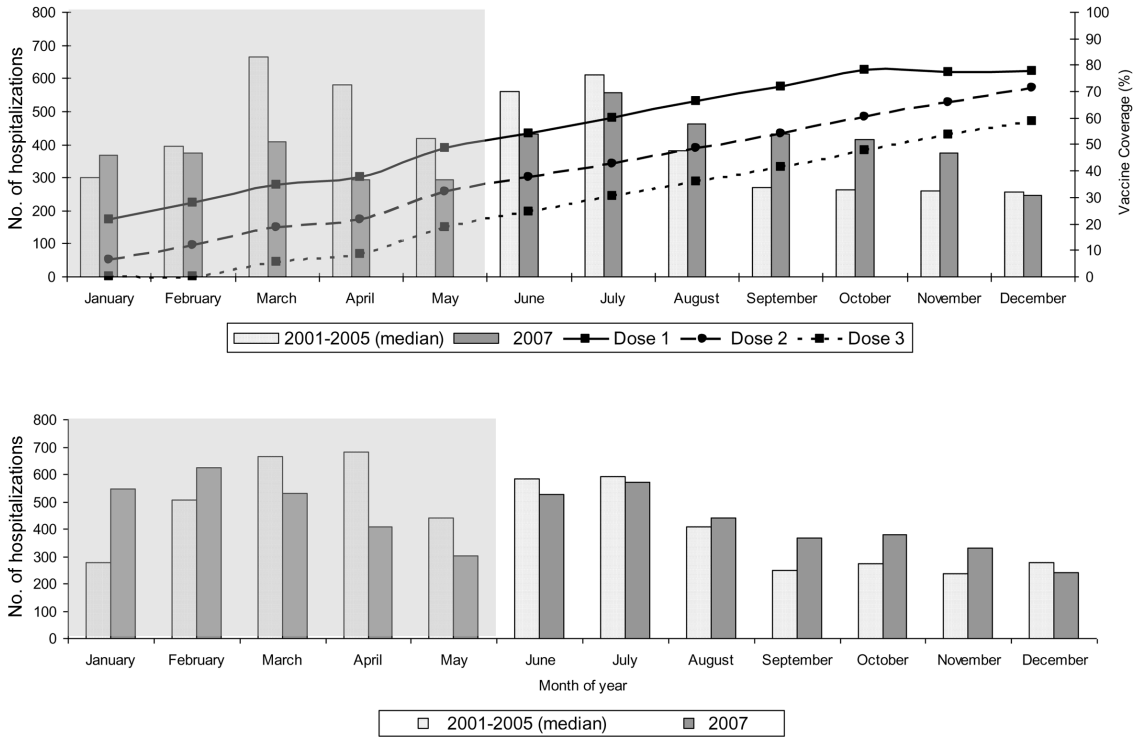

Figure 3. Vaccine coverage among children aged 0–11 months *(top)* and comparison of the median number of monthly hospitalizations for acute gastroenteritis during 2001–2005 and 2007 among vaccinated children (age, 0–11 months; *top*) and unvaccinated children (age, 12–59 months; *bottom*) in Nicaragua. Vaccine coverage is presented as the percentage of coverage in the total population of children aged 0–11 months. The shaded area (from January through May) represents the annual rotavirus season in Nicaragua [10, 14].

decrease in the number of hospitalizations for AGE was noted among children aged 0–11 months, whereas a ~5% increase was observed among children 12–59 months of age. Although a greater decrease in the number of episodes of AGE among vaccine-eligible children aged 0–11 months than among non-eligible older children suggests possible beneficial effects of vaccine, vaccine coverage was relatively low among all children aged 0–11 months during the 2007 season, and it is difficult to derive firm conclusions because of yearly fluctuations in disease trends.

During future rotavirus seasons, substantially greater vaccine coverage should be achieved among infants and, subsequently,

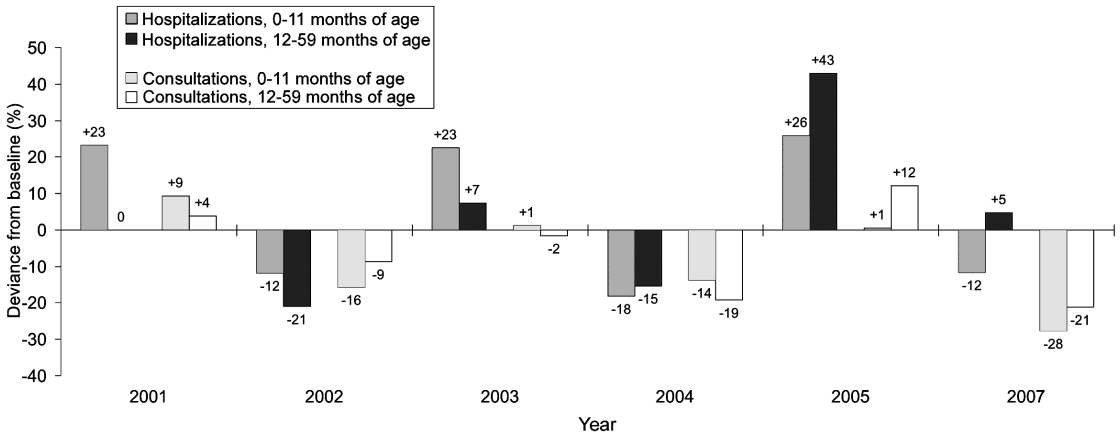

Figure 4. Yearly change from baseline of total consultations and hospitalizations for acute gastroenteritis among children aged <1 year and children aged 2–5 years during the rotavirus seasons, 2001–2007, Nicaragua. Baseline estimates were based on the mean number of events from January through May during 2001–2005, excluding the year in question. Data from 2006 were not used because a nationwide health care worker strike prevented the accumulation of appropriate surveillance data for analysis.

older children, and further monitoring of age-specific data on trends in AGE and correlation of these data with vaccine coverage will be useful in monitoring the impact of a vaccine program. It is anticipated that the reductions in the rate of AGE as a result of the direct protective effects of vaccination will be greatest among children aged 0–11 months in 2008 and will extend successively to older children in future seasons. However, unless large reductions in rates are noted, the yearly fluctuations in AGE trends may pose substantial challenges when relying on nonspecific indicators of outcome, such as all-cause diarrhea, to monitor the impact of a vaccine program. From an operational standpoint, the value of a vaccine program might be better assessed through epidemiologic studies to more directly assess vaccine effectiveness (eg, case-control method) and through monitoring of disease trends at sentinel surveillance sites where rotavirus testing is conducted for most children admitted with diarrhea. In early 2007, we established such a surveillance system at 4 hospitals in Nicaragua, and a recently published vaccine effectiveness study at these sites identified that RotaTeq vaccination prevented 50% of the rotavirus-related hospitalizations [15]

Several caveats must be considered when interpreting our findings. First, our data do not include private hospitals and clinics. However, >85% of the Nicaraguan population uses public facilities that report to the Ministry of Health. Second, although vaccine coverage is likely to be high in Nicaragua, previous surveys suggest that the administrative method may provide inaccurately higher estimates of vaccine coverage because of monthly variations in the birth cohort or imprecise estimates of the population and the number of doses administered [11, 12, 16]. Third, although we noted a decrease in trends in the number of episodes of diarrhea, precise postlicensure vaccine effectiveness for the rotavirus vaccines remains unknown and is particular important to assess because RotaTeq has predominantly been tested in the higher socioeconomic populations of Finland and the United States; the performance of the vaccine in a low-income setting might be quite different [4, 8].

In conclusion, data on vaccine uptake suggest that RotaTeq was successfully integrated in the existing immunization program in Nicaragua, the first GAVI-eligible low-middle–income country to adopt the vaccine. Ongoing surveillance for AGE and, specifically, for AGE caused by rotavirus and vaccine effectiveness studies are necessary and will provide a more accurate assessment of the public health benefits of vaccination. Countries considering rotavirus vaccine introduction will greatly benefit from establishing active surveillance programs for monitoring rotavirus diarrhea at sentinel hospitals according to the World Health Organization generic protocol for rotavirus surveillance [17], and such surveillance should ideally be established 2–3 years before vaccine introduction to provide good baseline estimates for assessment of vaccine impact.

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