

The epidemiology of rotavirus diarrhea in Latin America. Anticipating rotavirus vaccines

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ABSTRACT

Objective. To assess the disease burden and characterize the epidemiology of rotavirus diarrhea in Latin America.

Methods. We conducted a literature review of studies of children < 5 years of age who were hospitalized or seen as outpatients for diarrhea and for whom rotavirus was sought as the etiologic agent of the diarrhea. This review included inpatient and outpatient studies published since 1998 that included at least 100 children and reported surveillance activities lasting at least 12 consecutive months.

Results. A total of 18 inpatient and 10 outpatient studies met the criteria for inclusion in this review. Rotavirus was detected in a median of 31% of inpatients (range, 16%–52%) and 30.5% of outpatients (range, 4%–42%). The median detection rate was higher in studies that used an enzyme-linked immunosorbent assay (ELISA) (inpatients 38%, outpatients 33%) versus less sensitive methods of detection. The age distribution of rotavirus disease varied among countries, with 65%–85% of children hospitalized in the first year of life. Most countries had rotavirus admissions year round, and rotavirus generally exhibited a winter seasonal peak in both temperate and tropical climates.

Conclusions. The heavy burden of disease attributable to rotavirus in Latin America suggests that vaccines currently being tested could have considerable impact in preventing hospitalizations, clinic visits, and deaths. The findings of the young age distribution of patients highlight the importance of early immunization for the success of a vaccine program. The data suggest that future surveillance for rotavirus diarrhea in Latin America should use a standardized surveillance protocol with an ELISA for detection. Data from surveillance studies will be critical to monitor the impact of the future introduction of vaccines.

Key words

Rotavirus; disease outbreaks; burden of illness; epidemiology; Latin America.

Severe gastroenteritis caused by rotavirus is a leading cause of childhood

illness and death, particularly in developing countries. Each year, rotavirus infections claim the lives of approximately half a million children worldwide and lead to an estimated 2 million hospitalizations, 25 million clinic visits, and 111 million episodes of diarrhea in children < 5 years of age (1). Because the disease cannot be eliminated through improvements in water

and sanitation, vaccines have been developed as the prime method of control (2–4). Two vaccines nearing licensure aim to prevent severe disease leading to dehydration, hospitalization, and death. The accelerated development and introduction of a rotavirus vaccine has been designated a global priority by the World Health Organization, the Global Alliance for Vac-

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cines and Immunization, and many international groups because the burden of disease is large, vaccines are close at hand, and the impact of their introduction should be almost immediate (5).

Latin America is likely to be the first region in the developing world to be targeted for the introduction of a rotavirus vaccine. Both vaccines nearing licensure are being tested in the region, and for new vaccines, like those for Hepatitis B and *Haemophilus influenzae b*, Latin America has been the first site in the developing world to embrace their introduction. Yet despite the impending availability of rotavirus vaccines, knowledge of the epidemiology and disease burden of rotavirus in the Region remains limited, and many policymakers are unaware of the high prevalence of this disease. This is not surprising, since despite the broad recognition of the importance of childhood diarrhea, physicians rarely seek rotavirus as the etiologic agent because knowledge of the pathogen does not alter treatment with rehydration therapy. Efforts to establish rotavirus surveillance in the Americas are ongoing, but to date, only limited data are uniformly available from a range of countries in the Region spanning a full year or more.

In anticipation of the need for better estimates of the disease burden of rotavirus and more comprehensive epidemiologic information, as well as background data to establish a rotavirus surveillance network in the Region, we reviewed recent studies of rotavirus disease among children in Latin America published between 1998 and 2003. The objectives of this review were to examine the disease burden, the rate of detection of rotavirus among children with diarrhea who were hospitalized or visited outpatient clinics, and the age distribution and seasonality of rotavirus infection.

METHODS

For this review, we identified papers from a multilingual MEDLINE search of publications, using the keyword "rotavirus" and the name of 43 Latin American countries, and from citations noted in studies found through the

MEDLINE search. From these studies, we extracted information on the detection rate of rotavirus and methods used, the location, duration, and size of the study, and the age of the children enrolled. The studies were grouped by setting—inpatient or outpatient—and analyzed separately, since rotavirus detection rates vary significantly by severity of illness, with the highest detection rates reported among hospitalized children with more severe disease. For inpatient and outpatient settings, we limited the review to those studies published since 1998 that included at least 100 children < 5 years of age and that reported surveillance activities lasting at least 12 consecutive months. All methods of rotavirus detection were considered, including enzyme-linked immunosorbent assay (ELISA), polyacrylamide gel electrophoresis (PAGE), and latex agglutination (LA).

For those studies that provided detailed information on the ages of patients < 3 years of age, we plotted and compared the distribution of rotavirus cases by age groups: 0 to 5, 6 to 11, 12 to 23, and 24 to 35 months. Seasonal and geographical trends in rotavirus diarrhea were reviewed from studies presenting detailed information about monthly detection for at least one calendar year. To determine the peak season, we plotted the rotavirus detection rates by month and defined peaks as a period of 3 months or more in which the rate of detection was consistently above the yearly median for the 12-month period.

RESULTS

Overview of inpatient and outpatient studies

We identified 18 studies of children hospitalized for gastroenteritis that met the criteria for inclusion in this review (Table 1). Overall, rotavirus was detected in a median of 31% of children, and the detection rates ranged 3-fold between studies, from 16% to 52%. To understand this variability, we compared rates of detection, stratifying by assay method, age of patients enrolled, and size and duration of the study. The assay method clearly affected the detection rates, and the 12 studies that used

ELISA reported higher rates of rotavirus (median 38%, range 16%–52%) than the five that did not (median 24%, range 16%–32%). This difference was not statistically significant for the inpatient studies alone but was significant when combined with data from the 10 outpatient studies. We then examined whether rates of hospitalization were associated with the size or the duration of the study or with the patients' ages. The rates of detection by ELISA were slightly lower for longer studies when compared with shorter ones, but the size of the study did not affect detection rates. Surprisingly, the age cutoff did not affect detection rates; the nine studies that enrolled children < 5 years of age had rates of rotavirus detection similar to those of studies limited to children < 3 years old.

We examined the characteristics of six studies reporting rates at the extremes of the range—four with detection rates < 20% and two with rates \geq 50%. Rotavirus usually spares children in their first few months of life, and three of the four studies with low detection rates included an unusually large number of young infants. The Brazil study was conducted at a center that focused on neonatal care, and 47% (48/102) of samples were from infants < 6 months of age (6). The Venezuela study enrolled children < 5 years old, but nearly two-thirds were < 1 year of age (7). The study from Uruguay included children \geq 20 months old, with a mean age of 4–5 months (8). In addition, this study investigated diagnoses of both "persistent" and "acute" diarrhea, whereas rotavirus is associated with acute diarrhea alone. Two of the low-reporting studies (7, 9) used the less sensitive PAGE system for detection. We could not identify a plausible explanation for the high rates of \geq 50% reported by two studies (10, 11).

Ten studies of children with gastroenteritis who were treated as outpatients met the criteria for inclusion in this review (Table 2). The rates of detection for these studies ranged 10-fold from 4% to 42%, with a median of 30.5%. Again, detection rates in the two studies that used PAGE for detection were lower (median 12%, range 4%–20%) compared with rates for the eight that used ELISA (median 33%, range

TABLE 1. Rotavirus detection rates from 18 studies (published from 1998 to 2003) of children hospitalized^a for gastroenteritis in Latin America^b

Country	Reference	Study characteristics			Patient characteristics		
		Years of enrollment	Duration (months)	Detection assay ^c	Number	Age (years)	% with rotavirus
Argentina	20	1996–1998	24	ELISA	1312	<3	42
	21	1997–1998	12	ELISA	133	<3	35
Brazil	22	1986–2000 ^d	154	ELISA	1113	<2	30
	6	1995–1996	18	ELISA	102	<5	16 ^e
	23	1992–1994	24	ELISA	181	<5	21
	24	1998–1999	24	PAGE	212	<5	29
Chile	18	1997–1999	24	ELISA	276	<3	47
Colombia	25	1995–1996	12	PAGE	131	<5	32
Paraguay	26	1999–2000	14	ELISA	141	<3	43
	9	1998–2000	36	PAGE	393	<3	19
Peru	10	1995–1997	12	ELISA	381	<5	52
Uruguay	8	1990–1994	48	ELISA	224	<2	19
Venezuela	18	1997–1999	24	ELISA	946	<3	38
	27	1992–1993	12	ELISA	557	<3	43
	28	1993–1995	23	LA	464	<5	24
	7	1993–1995	24	PAGE	379	<5	16
	11	1992–1993	12	ELISA	321	<5	50
	31	1993–1995	24	ELISA	2552	<5	30
Median (range)			24 (12–154)		350 (102–2552)		31 (38) ^f (16–52)

^a Includes studies in which children are identified in emergency departments or oral rehydration clinics.

^b Includes studies with ≥ 100 children continued for ≥ 1 year.

^c ELISA = enzyme-linked immunosorbent assay; PAGE = polyacrylamide gel electrophoresis; LA = latex agglutination.

^d With the exception of years 1995–1997.

^e Study emphasizing neonatal rotavirus with 47% in 0–5 month age group.

^f 38% for 13 studies using ELISA as the detection method.

18%–42%). The number of children included in the study ranged from 106 to 2 929, with a median of 724, and the detection rate was not associated with study size. Likewise, neither the age cutoff nor the duration of study correlated with detection rates. The most notable outlier, the Brazilian study with a rotavirus detection rate of 4%, used the less-sensitive PAGE method and enrolled two patient populations: private patients who had a detection rate of less than 3% and public health patients whose detection rate was 29%. The study with the highest outpatient detection rate of 42% occurred in a prepaid clinic that served patients of a different socioeconomic background than the general population (12).

Age of patients with rotavirus diarrhea

To investigate the age distribution of children with rotavirus diarrhea, we identified five studies that provided detailed age data on the patients studied (Figure 1). The cumulative frequency

distribution of children with rotavirus was plotted by age, and we identified substantial variability. The curves for Venezuela and Colombia were steeper and to the left of those for Argentina, Paraguay, and Brazil, indicating that patients were younger. By 6–11 months of age, nearly 80% of children in Colombia and Venezuela, versus 40%–50% of children in Argentina, Brazil, and Paraguay, had sought care for rotavirus diarrhea. Furthermore, if a vaccine were available but not administered until 5 months of age, 40% of all rotavirus cases in Venezuela and 25% of all cases in Colombia would not be prevented. A finding of note was that the two countries with the youngest age distribution were both in the tropics rather than in the temperate zone.

Seasonality of rotavirus infection

We examined the seasonal patterns of disease by plotting the monthly detection of rotavirus in the studies that provided detailed data on rotavirus hospitalization by month (Figure 2).

The 10 studies that were identified spanned latitudes from 10° north to 35° south. In most countries, rotavirus was detected throughout the year. The only locations where rotavirus was not detected for 2 consecutive months were Juiz de Fora and Porto Alegre in Brazil. We examined the hypothesis that the seasonality of rotaviruses was distinct in countries located in temperate versus tropical climatic zones. The five studies from cities in the tropics (between 23.5° north and south of the equator) all had winter peaks not unlike the five studies from cities in the temperate zone. As expected, the winter peaks in the northern hemisphere occurred roughly between November and February, while the peaks in the southern hemisphere occurred between May and August.

DISCUSSION

In Latin America, rotavirus remains the major cause of hospitalization and outpatient visits for children with diarrhea. This review of 28 studies of children hospitalized for severe diar-

TABLE 2. Rotavirus detection rates from 10 studies (published from 1998 to 2003) of children seen as outpatients for gastroenteritis in Latin America^a

Country	Reference	Study characteristics			Patient characteristics		
		Years of enrollment	Duration (months)	Detection assay ^c	Number	Age (years)	% with rotavirus
Argentina	30	1997–1998	12	ELISA	648	<3	36
	18	1997–1999	24	ELISA	1133	<3	39
Brazil	31	1996–1998	24	ELISA	494 ^c	<5	18
	24	1998–1999	24	PAGE	844	<5	4
	32	1997–1999	34	PAGE	646	<5	20
Chile	18	1997–1999	24	ELISA	1739	<3	34
Uruguay	33	1996–1999	48	ELISA	800	<2	32
	12 ^d	1997–1998	12	ELISA	106	<5	42
Venezuela	27	1992–1993	12	ELISA	363	<3	21
	18	1997–1999	24	ELISA	2929	<3	29
Median (range)			24 (12–48)		724 (106–2929)		30.5 (33) ^e (4–42)

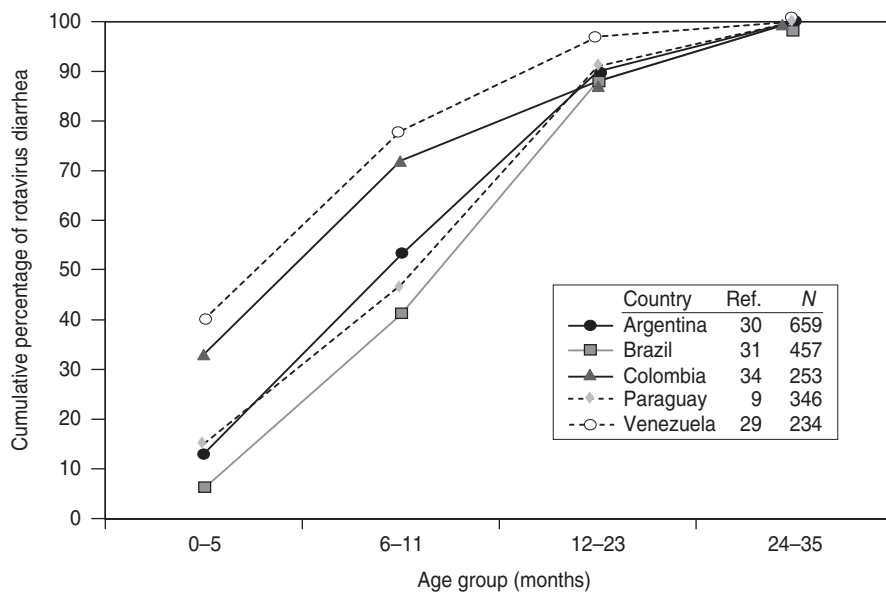
^a Includes studies with ≥ 100 children continued for ≥ 1 year.

^b ELISA = enzyme-linked immunosorbent assay; PAGE = polyacrylamide gel electrophoresis.

^c Represents the subset of total study data that includes children ≤ 5 .

^d Data gathered at prepaid a clinic that serves a different population from that of the public hospital.

^e 33% for 8 studies using ELISA as the detection method.

FIGURE 1. Cumulative percentage of children with rotavirus diarrhea by age

rhea in eight Latin American countries identified rotavirus as the cause of disease in 31% of patients in the studies that used any assay and in 38% of patients in the studies that used the more sensitive ELISA. In general, rotavirus is detected less frequently in children with milder disease, so we were surprised to find that the rate of detection among children with diarrhea seen as outpatients (30.5%) did not differ greatly from that among children who

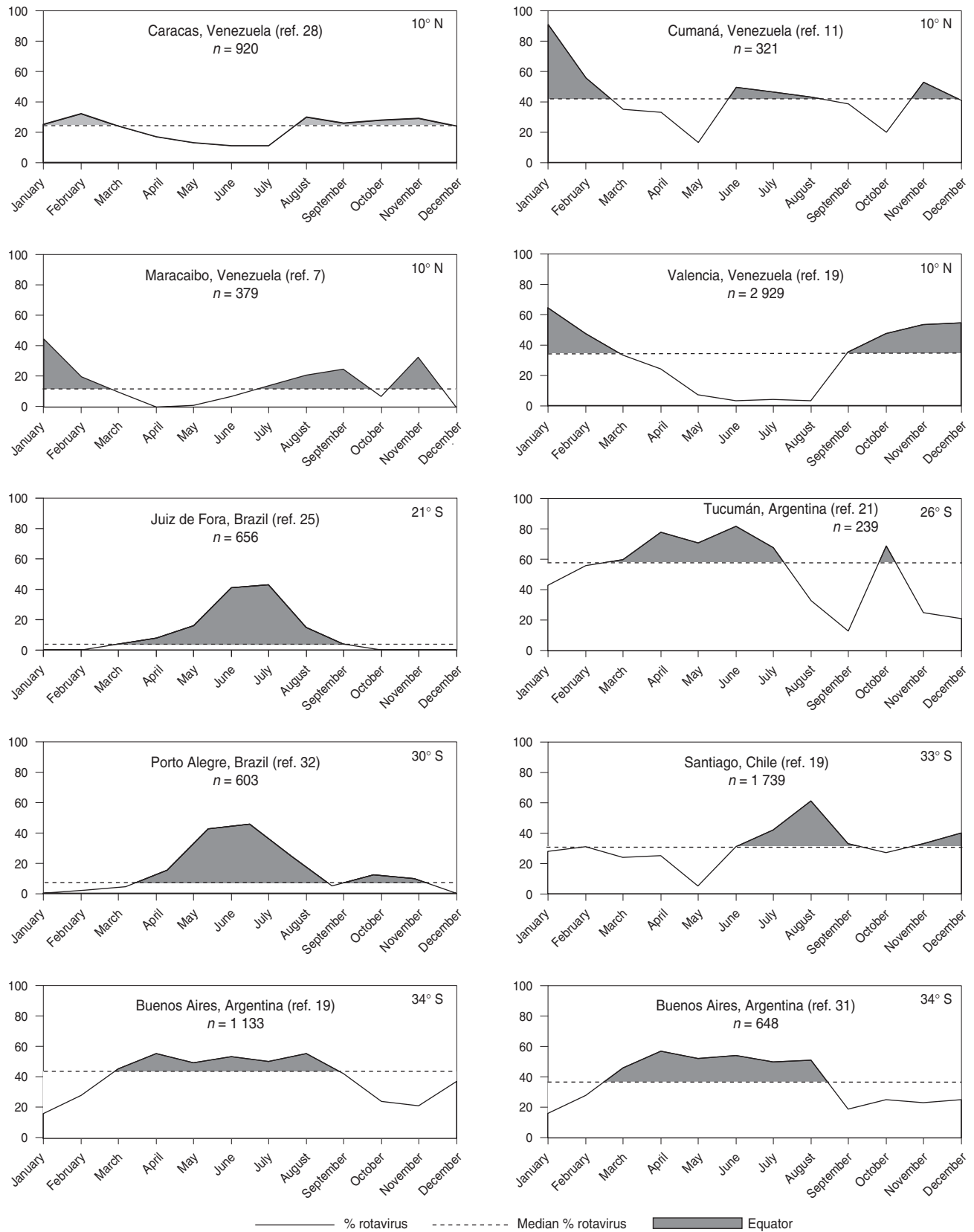
were hospitalized with more severe disease. Most children were hospitalized during their first year of life, and 90% of all rotavirus hospitalizations were among children < 2 years of age. Although rotavirus infections had a distinct seasonal peak in most countries, most countries also had rotavirus admissions year round.

Several features of rotavirus epidemiology and surveillance were identified in this review that have impli-

cations for future surveillance and further study. First, studies that used ELISA for detection had rates of rotavirus that were higher than studies that used less sensitive methods, an observation on diagnostic sensitivity noted previously (13–15) and evident from our results. Second, we found two different age distributions: in two tropical countries, nearly 90% of the children were hospitalized in the first year of life, whereas in the three countries with temperate climates, rotavirus occurred significantly later. We could not gather enough information from the remaining studies to determine whether this relationship to latitude was significant and thus would need to confirm this in prospective surveillance studies now being planned. Nonetheless, the early age of illness—with 20%–60% of rotavirus cases occurring by 6 months of age—indicates that vaccination early in life will be important to realize the greatest benefit from the vaccine.

The detection rates of hospitalization for rotavirus in our study (31%–38%) were intermediate between a multi-country surveillance study recently conducted in Asia (45%) and a similar literature review from Africa (24%) (16, 17). This difference in rates may reflect the prevalence of competing pathogens that are also responsible for hospitalization

FIGURE 2. Percentage monthly rate of cases of diarrhea with excretion of rotavirus in Latin American countries. The yearly median is marked; the shaded areas indicate peaks above the median value



for severe diarrhea, with the highest incidence of other organisms appearing in children in Africa. Within Latin America, a recent multicenter study in three countries found rates of hospitalization for rotavirus that ranged 2-fold from 38% in Venezuela to 70% in Argentina (18). Of note was that the rate of rotavirus detection was inversely proportional to the size of the study populations, with < 100 patients enrolled in Argentina but > 1 000 in Venezuela. The rate for Venezuela, the site providing most of the data, was very close to our estimate for Latin America. Finally, a recent series of industry-supported studies of the prevalence of hospitalizations for rotavirus in 11 countries in Latin America, which were done in anticipation of the vaccine trials conducted by GlaxoSmithKline, identified rates of rotavirus detection of 49%, with substantial variability between countries and months of observation (19). Rates in these studies are difficult to compare because none of these studies spanned a full year and many included the season in which rotavirus infection would be expected to reach its peak.

A main limitation of this study is that we focused on large, recently pub-

lished studies that were conducted in large, richer countries; studies from the poorer and smaller countries in the Region, where the pattern of disease may be different, are underrepresented. For some countries such as Mexico, many excellent studies were conducted before the starting date for the current review. Therefore, our observations, while interesting, do not provide an exhaustive picture of the epidemiology in all 43 countries of the Region but only glimpses of the disease burden in eight of the larger countries.

This review provides some important guidelines for establishing further surveillance of rotavirus in Latin America. First, it is clear that future studies should rely exclusively on the more sensitive ELISA rather than other competing detection methods. Furthermore, surveillance needs to be conducted for time periods of years to avoid biases from recruiting only in a high or low season. More data from poor or small countries could make the results more representative and help identify whether real differences exist by size or by per capita income. A question this study leaves unanswered is whether more children experience ro-

tavirus in their first year of life in tropical climates compared to temperate climates—a characteristic that might influence the value of earlier vaccination. Use of a uniform generic protocol for sentinel hospital surveillance with standard detection methods would not only aid further assessments of the current rotavirus disease burden, but would also provide a robust means for monitoring the impact of vaccines when they are introduced (19). Communication of these results on a monthly basis might further enhance awareness of this common and important childhood disease, which may soon be preventable by vaccination.

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RESUMEN

La epidemiología de la diarrea por rotavirus en América Latina. Perspectivas de vacunación frente al rotavirus

Objetivo. Valorar la carga de enfermedad e identificar las características epidemiológicas de la diarrea causada por rotavirus en América Latina.

Métodos. Realizamos una revisión de la literatura que abarcaba los estudios de niños menores de 5 años que fueron hospitalizados o atendidos como pacientes ambulatorios a causa de la diarrea, y en los cuales se buscó al rotavirus como agente etiológico de la diarrea. Nuestro trabajo de revisión incluye los estudios publicados desde el año 1998 sobre pacientes ingresados y ambulatorios, que incluyeron a 100 niños o más, y que informaron sobre actividades de vigilancia que se prolongaron durante al menos 12 meses consecutivos.

Resultados. Un total de 18 estudios de pacientes ingresados y 10 estudios de pacientes ambulatorios satisficieron los criterios de inclusión de nuestro trabajo de revisión. Se detectó el rotavirus en el 31% (mediano) de los pacientes ingresados (intervalo del 16% al 52%) y en el 30.5% de los pacientes ambulatorios (intervalo del 4% al 42%). La tasa mediana de detección fue mayor en los estudios que emplearon un ensayo de encimoinmunoanálisis (ELISA) (pacientes ingresados: 38%, pacientes ambulatorios: 33%) frente a otros métodos de detección menos sensibles. La distribución de la enfermedad rotavírica según la edad difería entre países, aunque la proporción de niños hospitalizados durante el primer año de vida fue del 65% al 85%. En la mayoría de los países se produjeron ingresos hospitalarios por rotavirus durante todo el año, y el rotavirus normalmente mostraba un máximo estacional en el invierno tanto en las zonas de clima tropical como en aquellas de clima templado.

Conclusiones. La importante carga de enfermedad que se atribuye al rotavirus en América Latina sugiere que las vacunas que están siendo ensayadas en la actualidad podrían tener un impacto considerable en la prevención de las hospitalizaciones, consultas a los centros de salud, y muertes. La distribución de la enfermedad entre los pacientes más jóvenes subraya la importancia de la inmunización precoz en el éxito de los programas de vacunación. Los datos sugieren que en el futuro, los programas de vigilancia para detectar la diarrea causada por rotavirus en América Latina deberían usar un protocolo normalizado de vigilancia con ELISA para la detección del virus. Los datos provenientes de estudios de vigilancia serán de importancia fundamental para el seguimiento del impacto de la introducción de vacunas en el futuro.