SUPPLEMENT ARTICLE

Sentinel Hospital Surveillance for Rotavirus Diarrhea in the People's Republic of China, August 2001–July 2003

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China has the second largest birth cohort in the world and the second highest number of deaths due to rotavirus infection. It is also the only country with a licensed rotavirus vaccine. Chinese policy makers now need credible estimates of the burden of rotavirus disease, to decide about vaccine use. From August 2001 through July 2003, prospective hospital-based surveillance for rotavirus diarrhea among children <5 years of age was conducted in 6 sentinel hospitals. Rotavirus isolates were characterized to determine the G and P genotypes circulating during the study. Of 3149 children who were admitted to the hospitals for diarrhea and for whom screening for rotavirus was performed, 1590 (50%) had positive results of an antigen detection assay. Of all episodes of rotavirus diarrhea, 95% occurred during the first 2 years of life. The most common rotavirus strain was P[8]G3 (49% of episodes), and all the common strains were detected, including G9 strains (4% of episodes). Ongoing efforts are under way to more precisely define the burden of rotavirus diarrhea in urban and rural populations, to assess the proportion of episodes that may be due to unusual or emerging strains, and to estimate the economic burden of rotavirus disease.

A critical step toward the development of a rational immunization policy for the use of rotavirus vaccines for Chinese infants [1] will involve establishing the burden of rotavirus diarrhea. Although previous epidemiologic studies in China identified rotavirus infection as the leading cause of diarrhea in childhood, they were of limited value because they covered different study periods (e.g., a 6-month period vs. a 12-month period), diagnostic tests (e.g., latex agglutination vs. EIA), age groups (infants only vs. infants plus older children), and case definitions [2–4].

Standardized surveillance for rotavirus diarrhea was needed to provide data that could be used to make national policy decisions regarding the introduction of rotavirus vaccine into the routine schedule of immunization of infants. It was clear that such data were particularly important because China has the second largest birth cohort in the world and is the only country with its own licensed rotavirus vaccine. We conducted prospective surveillance of children admitted to 6 hospitals in China, using the World Health Organization Generic Protocol and a standard immunoassay. The results of the present study provide the foundation for

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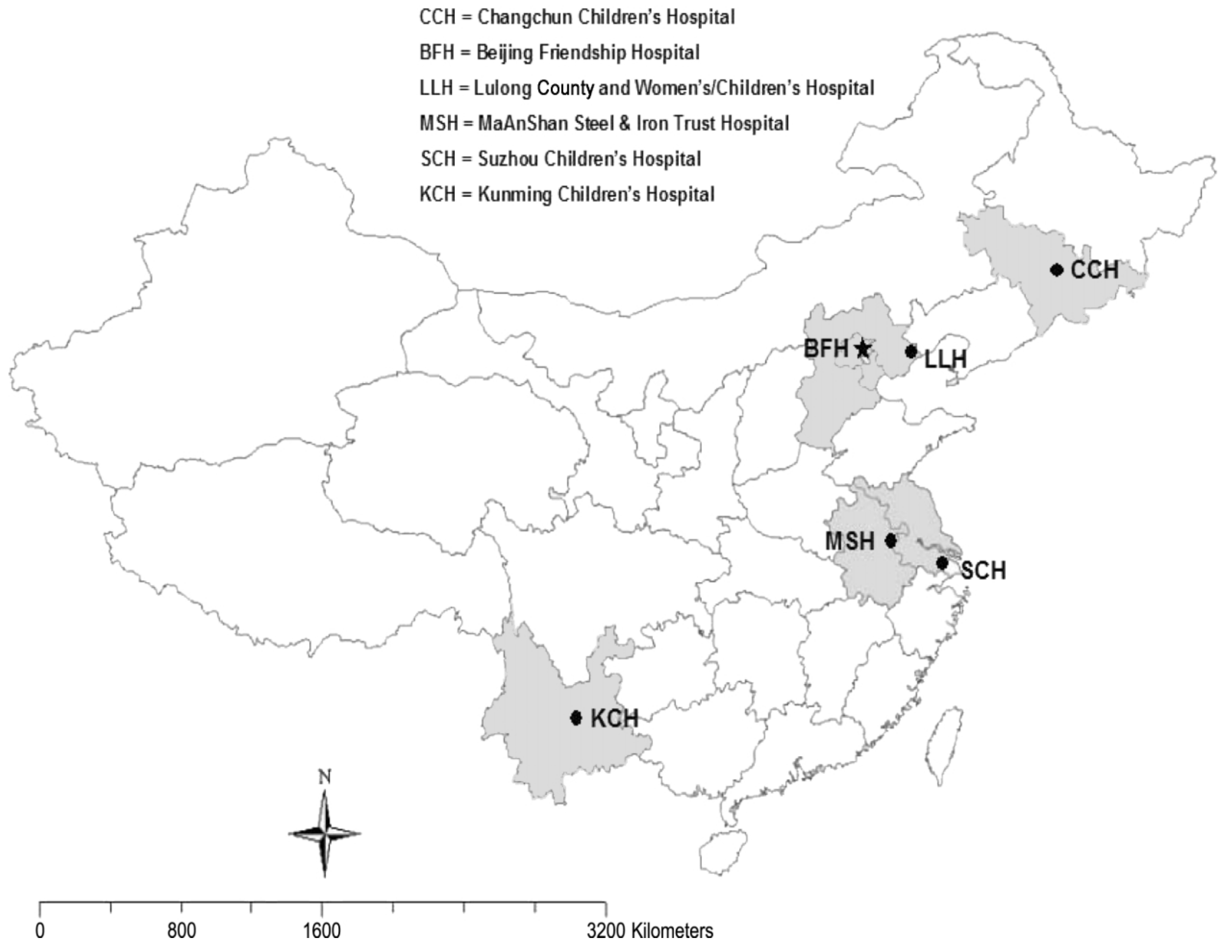

Figure 1. Locations of the 6 sentinel hospitals for rotavirus surveillance, People's Republic of China, 1 August 2001–31 July 2003

the development of national estimates of the burden of rotavirus diarrhea.

MATERIALS AND METHODS

Sentinel study hospitals. The 6 hospitals that were identified from representative population centers in China either were major children's hospitals or had a separate pediatric department (figure 1). In the north, the hospitals participating in the study included the Changchun Children's Hospital (a county hospital); Beijing Friendship Hospital (the pediatric department of a general hospital); and Lulong County and Women's and Children's Hospital (for which the coordinator of the study was the Lulong County Center for Disease Control and Prevention). In the south, the participating hospitals were Kunming Children's Hospital; MaAnShan Steel and Iron Trust Hospital, and Suzhou Children's Hospital. Hospitals were selected on the basis of their geographic location, the provision of services to a large population of children, the previous experience of investigators with surveillance, and the local clinicians' ability to collect patient data and clinical specimens during a 2-year study [5, 6].

The present study was reviewed and exempted from human subjects review at the Centers for Disease Control and Prevention (Atlanta, GA) and at the Institute of Virology, Chinese Academy of Preventive Medicine, Beijing, Peoples' Republic of China. The study was approved by the institutional review boards of all the surveillance sites.

Rotavirus surveillance system. Children were evaluated for signs and symptoms of diarrhea, by use of standardized clinical criteria, and parents were asked to obtain a fresh stool specimen from their child and provide it for rotavirus testing. The criteria for inclusion of children in the present study were (1) age <5 years, (2) presence of diarrhea at the time of clinical presentation, and (3) admission to the diarrheal treatment unit, emergency department, or inpatient ward. A case of diarrhea was defined by the presence of ⩾3 liquid stools in a 24-h period. Stool specimens were labeled with the date of collection and a unique surveillance identification number, to permit report-

Table 1. No. of admissions to the hospital for diarrhea and rotavirus diarrhea among children aged <5 years, People's Republic of China, 1 August 2001–31 July 2003.

Location	Hospital	Total no. of patients enrolled	No. (%) of patients with stool specimens screened[a]	Patients with rotavirus-positive stool specimens	
				No.	%[b] (95% CI)
MaAnShan City, Anhui Province	MaAnShan Steel and Iron Trust Hospital	187	158 (84)	44	28 (21–35)
Beijing municipality	Beijing Friendship Hospital	137	70 (51)	25	36 (24–47)
Lulong County, Hebei Province	Lulong County Hospitals[c]	1178	667 (57)	297	46 (41–48)
Suzhou City, Jiangsu Province	Suzhou Children's Hospital	864	703 (81)	341	49 (45–52)
Changchun City, Jilin Province	Changchun Children's Hospital	1634	904 (55)	588	65 (62–68)
Kunming City, Yunnan Province	Kunming Children's Hospital	1642	647 (39)	295	46 (42–49)
All		5642	3149 (56)	1590	51 (49–52)

NOTE. CI, confidence interval.

[a] Percentage of patients tested among the total no. of patients enrolled at each hospital.

[b] Percentage of patients with rotavirus-positive stool specimens among the total no. of patients who had stool specimens screened at each hospital.

[c] A county hospital and a women's and children's hospital.

ing of test results to pediatricians. Study investigators received monthly reports of patients enrolled in surveillance at each sentinel hospital, reviewed data forms for completeness, and periodically monitored field sites to ensure data quality.

Laboratory testing for rotavirus. All stool specimens were frozen (at −20°C) and stored for testing. The specimens were then shipped by air to the Viral Gastroenteritis Division of the Chinese Center for Disease Control and Prevention in Beijing every month during the rotavirus season and every 2 months outside the peak rotavirus season. Our goal was to test ~300 specimens per center each year. Before testing, an unstratified sample consisting of ~3 of every 4 stool specimens was identified for rotavirus testing. Stool specimens were tested for group A rotavirus by use of a commercial immunoassay (Rotaclone; Meridian Diagnostics). A subset of these rotavirus strains was further characterized for G and P type by use of reverse-transcription polymerase chain reaction (RT-PCR), as described by Gentsch et al. [7].

Data management and analysis. All hospitals were provided with identical forms for use in the collection of standardized data, and their staffs were trained for participation in the study. On a monthly basis, the forms were sent to the central

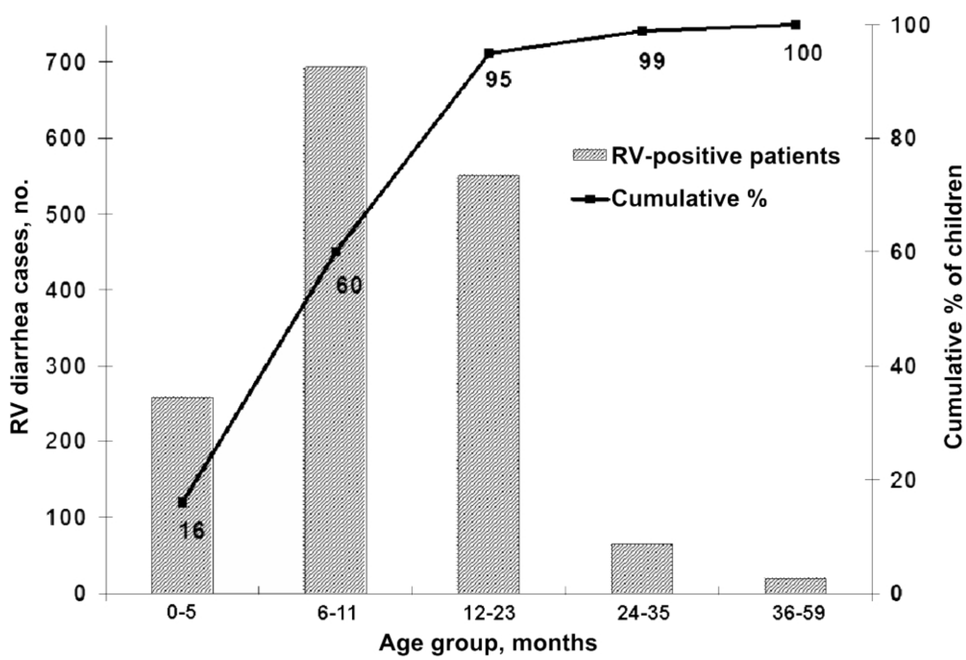

Figure 2. Cumulative age distribution of children <5 years of age who had rotavirus (RV) diarrhea (no. of RV-positive patients, 1590) and who were seen at 6 sentinel hospitals, People's Republic of China, 1 August 2001–31 July 2003.

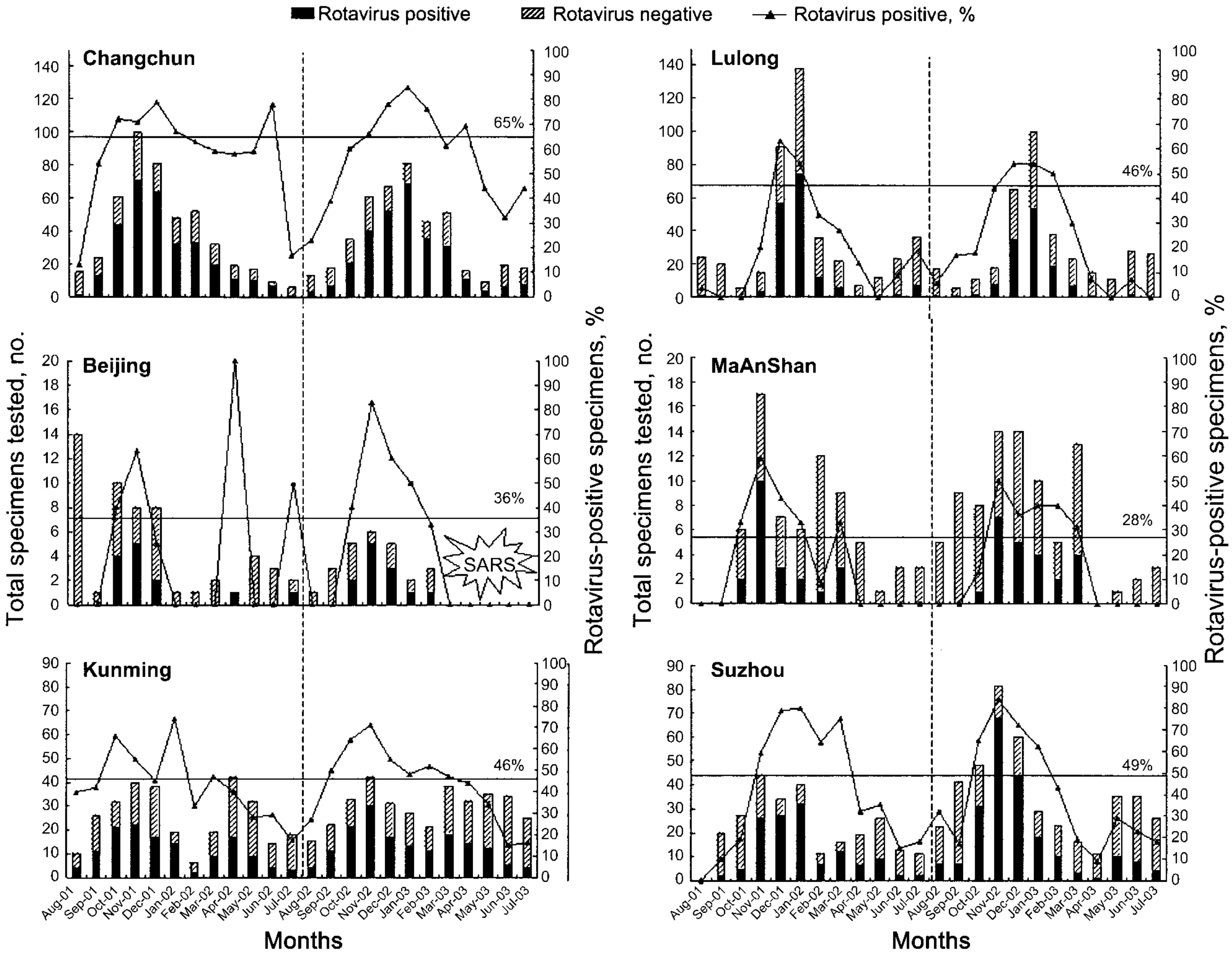

Figure 3. No. of admissions to the hospital for diarrhea each month *(bars)* and the percentages of rotavirus-positive specimens *(lines)* at 6 sentinel hospitals, for children aged <5 years, People's Republic of China, 1 August 2001–31 July 2003.

surveillance office where data were entered, and they were reviewed for completeness, accuracy, and consistency by use of a standard data-checking program. Laboratory results of G- and P-typing were merged with the database that contained routine demographic and clinical information. Categorical comparisons were performed using SAS statistical software (version 8.0; SAS). Rotavirus-positive children were compared with rotavirus-negative children to assess differences in the distribution of clinical signs and symptoms, and testing for statistical significance was performed using the χ^2 test or Fisher's exact test when the expected cell sizes were <5 [8]. Unadjusted risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using the Wilson score method [9].

RESULTS

Patients with diarrhea. From August 2001 through July 2003, a total of 5642 children were enrolled in the rotavirus surveillance system at the 6 sentinel hospitals. A stool specimen was collected from 4188 (74%) of all the children enrolled (table 1). The stool specimens obtained from 3149 (75%) of these 4188 children were tested for rotavirus by use of EIA antigen detection. A total of 1590 of the children who had testing performed were found to be rotavirus positive, and the proportion of children who were rotavirus positive ranged from 28% (in Anhui Province) to 65% (in Jilin Province).

We then examined the age distribution of patients with rotavirus diarrhea (figure 2). Among children hospitalized for rotavirus diarrhea, the rate of detection was highest for those aged 12–23 months (58% of children), followed by those aged 6–11 months (53%), 24–35 months (39%), 0–5 months (34%), and 36–59 months (15%). Overall, 95% of sick children were <2 years of age. Of the children with rotavirus diarrhea, 65% were boys and 35% were girls; these percentages were similar to the rates of hospitalization for diarrhea in general. Children with rotavirus diarrhea were 17% less likely to have been exclusively breast-fed, compared with rotavirus-negative children

Table 2. Genotypic distribution of rotavirus strains from sentinel hospital surveillance of children aged <5 years, People's Republic of China, 1 August 2001–31 July 2003.

	No. (%) of rotavirus strains, by G genotype							
P genotype	G1	G2	G3	G4	G9	G mixed	G NT	All
P4	18 (3.8)	21 (4.5)	35 (7.4)	…	7 (1.5)	4 (0.9)	6 (1.3)	91 (19.4)
P6	2 (0.4)	…	5 (1.1)	1 (0.2)	1 (0.2)	…	1 (0.2)	10 (2.1)
P8	40 (8.5)	2 (0.4)	232 (49.4)	1 (0.2)	12 (2.5)	7 (1.5)	19 (4.0)	313 (66.5)
P mixed	3 (0.6)	…	23 (4.9)	…	1 (0.2)	…	1 (0.2)	28 (6.0)
P NT	1 (0.2)	…	19 (4.0)	…	1 (0.2)	…	7 (1.5)	28 (6.0)
All	64 (13.6)	23 (4.9)	314 (66.8)	2 (0.4)	22 (4.7)	11 (2.4)	34 (7.2)	470 (100)

NOTE. The denominator used in the calculation of all percentages is the total no. of strains characterized (n = 470). Mixed, mixed G or P genotypes in 1 patient specimen; NT, nontypeable.

(RR, 0.83; 95% CI, 0.78–0.89). We observed no significant difference in the clinical severity of diarrhea between patients who were rotavirus positive and those who were rotavirus negative.

We plotted monthly data on rotavirus detection at each site, to identify trends in time and place (figure 3). The rotavirus season began in October and reached peaks in November, December, and January (with 66%, 65%, and 63% of patients found to be rotavirus positive, respectively). Geographically, we did not observe a clear geographic trend between sites that were farthest apart in southwestern China (Kunming) versus northeastern China (Changchun).

Rotavirus strain characterization. A total of 1396 rotavirus isolates were characterized by RT-PCR to determine G genotypes. The G3 serotype was the most common genotype overall (63% of isolates) and was found in each of the 6 participating sentinel hospitals; the G1 serotype was the second most common genotype (15% of isolates). G9 was found in only 3 of the 6 sentinel sites and was most common in Kunming, where 21 (78%) of all G9 strains were found. In addition, 15% of strains were G nontypeable. Among the strains that were G-typed, a representative subset of 470 isolates was also P-typed by RT-PCR (table 2). Of those 470 isolates, 313 (67%) were characterized as P[8]; 91 (19%), as P[4]; 10 (2%), as P[6]; and 28 (6%), as mixed P types. Twenty-eight strains (6%) remained nontypeable. The predominant strain P[8]G3 comprised 232 (49%) of all strains characterized. Other dominant strains were P[8]G1 (9% of strains), P[4]G3 (7%), P[4]G2 (5%), P[4]G1 (4%), and P[8]G9 (3%).

DISCUSSION

The present study is the first to use a common protocol to examine the prevalence of rotavirus as a cause of diarrhea in 6 widely separate regions of China during a common period. Our results demonstrate that rotavirus is the most common cause of diarrhea leading to hospitalization among children <5 years of age in China. Rotavirus was identified in 50% of the 3149 children who were <5 years of age, had diarrhea, and were enrolled in this surveillance study, and, between hospitals, the range of the detection rates was 28%–65%. Our finding is consistent with the findings of other hospital-based studies in China and elsewhere in Asia [6, 10–12]. Rotavirus infection occurred with a seasonal pattern typical of that seen in other countries, with peak activity (in October–March) beginning earliest (in October) in the southwest and later in other areas. Rotavirus was most commonly found in infants and children <24 months of age (accounting for 95% of all episodes of rotavirus diarrhea). This finding has important implications for the consideration of strategies for prevention through the routine immunization of children. That 16% of episodes of rotavirus diarrhea occurred in infants by the age of 6 months and that 60% of episodes occurred by 1 year of age suggest that protective immunity associated with vaccination should be achieved in the first 6 months of life and well before a child's first birthday, to prevent the greatest burden of rotavirus disease.

We were intrigued to find that the G3 serotype was the most common strain throughout China. It was previously identified in northern China but was less common in other countries and regions [13, 14]. Although P[8] was the most common P genotype, 49% of strains were P[8]G3, whereas only 15% of all strains that were G-typed were of the G1 serotype, which is the most commonly represented strain globally. Ongoing surveillance of rotavirus strains will be critical to understand the relative importance of homotypic and heterotypic protection after vaccination, to monitor for vaccine strains entering the community (such as the lamb vaccine strain), and to investigate the strains in children who experience vaccination failure and develop rotavirus diarrhea.

This large-scale study of rotavirus diarrhea in China has several limitations. Because of China's very large population, we were not able to include sentinel hospitals from every province. Thus, important population segments or minority populations may not be represented in the 6 study hospitals—in particular, children in the poorest provinces in the far west and these areas may have different circulating strains.

An important application of these surveillance data will be for advocacy related to immunization against and prevention of rotavirus diarrhea in China. Currently, rotavirus infection is rarely diagnosed, and most physicians and public health professionals are unaware of its importance. Directed efforts to increase awareness among pediatricians, public health scientists, and key public health decision makers will be critical to ensure that appropriate policies can be developed when new-generation rotavirus vaccines become available [15].

The findings of the present study suggest that clinic visits, visits for rehydration, and inpatient hospitalizations associated with diarrhea and rotavirus remain a common problem among Chinese children. At the same time, the few deaths detected in this large surveillance study suggest either that the mortality rate associated with diarrhea and rotavirus is very low in large urban areas or that children may die outside health facilities or hospitals. We are now pursuing additional information on deaths that may be associated with diarrhea in children. As China develops toward a market economy, health care costs will be borne by the public so that additional economic analysis may be required to better inform parents and decision makers about the costs and benefits of rotavirus vaccines.

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