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The Public Health Burden of Rotavirus Disease in Children <5 Years of Age and Considerations for Rotavirus Vaccine Introduction in China

Dan Wu, MD[1,*], **Catherine Yen, MD,MPH**[2,*], **Zun-Dong Yin, PhD**[1], **Yi-Xing Li, MD**[1], **Na Liu, PhD**[3], **Yan-Min Liu, MD**[1], **Hua-Qing Wang, MD,PhD**[1], **Fu-Qiang Cui, MD,PhD**[1], **Christopher J. Gregory, MD**[4], **Jacqueline E. Tate, PhD**[2], **Umesh D. Parashar, MBBS,MPH**[2], **Da-Peng Yin, MD,PhD**[1], and **Li Li, MD,PhD**[1]

[1]National Immunization Program, Chinese Center for Disease Control and Prevention, Beijing, China [2]Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, USA [3]Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China [4]Division of Global Health Protection, Centers for Disease Control and Prevention, Nonthaburi, Thailand

Abstract

Background: Rotavirus is the leading cause of severe diarrhea among young children worldwide. Rotavirus vaccines have demonstrated substantial benefits in many countries that have introduced vaccine nationally. In China, where rotavirus vaccines are not available through the national immunization program, it will be important to review relevant local and global information to determine the potential value of national introduction. Therefore, we reviewed evidence of rotavirus disease burden among Chinese children <5 years of age to help inform rotavirus vaccine introduction decisions.

Methods: We reviewed scientific literature on rotavirus disease burden in China from 1994 through 2014 in CNKI, Wanfang and Pubmed. Studies were selected if they were conducted for periods of 12 month increments, had more than 100 patients enrolled, and used an accepted diagnostic test.

Results: Overall, 45 reports were included and indicate that rotavirus causes ~40% and ~30% of diarrhea-related hospitalizations and outpatient visits, respectively, among children aged <5 years in China. Over 50% of rotavirus-related hospitalizations occur by age 1 year; ~90% occur by age 2 years. Regarding circulating rotavirus strains in China, there has been natural, temporal variation, but the predominant local strains are the same as those that are globally dominant.

Correspondence and reprints: Dr. Da-Peng Yin, MD PhD; Dr. Li Li, MD PhD,Chinese Center for Disease Control and Prevention, 27 Nanwei Road, Xuanwu District, Beijing 100050, China, yindp@chinacdc.cn, llsdjn@163.com.
*These authors contributed equally to this work.

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Conclusions: These findings affirm that rotavirus is a major cause of childhood diarrheal disease in China and suggest that a vaccination program with doses given early in infancy has the potential to prevent the majority of the burden of severe rotavirus disease.

Keywords

rotavirus; diarrhea; gastroenteritis; rotavirus vaccines

INTRODUCTION

Rotavirus is the most common cause of severe diarrhea in children worldwide [1]. Annually, it causes approximately 200,000–453,000 deaths [2], 2 million hospitalizations, and 25 million outpatient visits in children <5 years of age [3]. Currently, vaccination is the primary tool for prevention of rotavirus disease, and the World Health Organization (WHO) recommends that rotavirus vaccines be included in all national immunization programs as part of a comprehensive strategy to control diarrheal diseases [4]. In China, past studies have indicated that rotavirus infection accounts for ~40% of all acute gastroenteritis hospitalizations in children aged<5 years [5]. However, rotavirus vaccine currently is not included in the Chinese Expanded Program on Immunization (EPI) routine immunization schedule. As opposed to a vaccine provided through the EPI (also known as “Type 1” vaccines), a locally manufactured, live attenuated, oral, lamb rotavirus G10P[12] strain vaccine, Lanzhou Lamb Rotavirus (LLR) vaccine (Lanzhou Institute of Biological Products, Lanzhou, China), has been available on the private market since 2000 as a “Type 2” vaccine (i.e., a vaccine licensed for the manufacturer to sell in clinics or provider offices) [6].

Given the WHO recommendation for inclusion of rotavirus vaccines in all national immunization programs and the increasing evidence of the benefits of rotavirus vaccination in other countries [6], it will be important for decision makers to review relevant local and global information to determine the potential value of a national rotavirus vaccination program in China. This paper provides a comprehensive review of the scientific literature published over the last two decades on rotavirus disease burden and strain distribution in children <5 years of age in China, and considerations for vaccine introduction in China.

METHODS

Sources of data

For rotavirus disease burden estimates and strain distribution, we identified references through searches of PubMed and two Chinese literature databases (National Knowledge Infrastructure, China [CNKI] and Wanfang) for articles published from 1 January 1994 to 31 December 2014, by use of the terms (“rotavirus” and “China”) or (“diarrhea” and “China”). The term “China” was used for PubMed search only. Chinese language (”腹泻”或“轮状病毒”) was used for the CNKI and Wanfang searches. We then manually screened all English and Chinese language articles resulting from these searches for study population, study duration, and rotavirus diagnostic methods. Articles that met the following criteria were fully abstracted and included in this report: 1) data available for 100 or more patients <5 years of age; 2) study duration of at least 12 month increments (to account for seasonality of disease); and 3) use of the following rotavirus laboratory tests on fecal samples – enzyme-linked immunosorbent assay (ELISA) for rotavirus detection and/or reverse-transcriptase polymerase chain reaction (RT-PCR) for strain typing. We excluded literature reviews, studies reporting on adults only, and reports on outbreaks and nosocomial infections.

Categorization of rotavirus disease burden and strain distribution studies

We stratified rotavirus disease burden studies by health care setting (inpatient and outpatient) and by geographic location (urban and rural). For each study reviewed, we used a standardized form to abstract the rotavirus detection rate, health care setting, geographic location, study duration, and study population size. For inpatient studies that provided age-stratified data, we pooled the number of children enrolled by age to determine the cumulative age distribution for rotavirus-related hospitalizations. Since predominant rotavirus strains may change over time, we examined strain distribution by the following time periods for which data were available: 1995–1999, 2000–2004, 2005–2009, and 2010–2013.

RESULTS

Rotavirus disease burden

The initial search identified 10,342 rotavirus-related citations from CNKI, Wanfang, and PubMed. Forty-five studies met the inclusion criteria for review (Figure 1). Thirty-nine studies were published in Chinese, and six were published in English. Of the 45 included studies, 39 provided data on inpatient health care visits, with study periods ranging 12–60 months [7–45]and 10 provided data on outpatient health care visits, with study periods ranging 12–36 months [7, 8, 36, 42, 46–51].

For the 39 inpatient studies conducted between 1998 and 2013, a total of 74,846 (range per study: 169–14,511) children <5 years of age with acute gastroenteritis were evaluated (Table 1) for which a median of 44% (range: 7.3%−65.6%) of these children tested positive for rotavirus; the proportion of diarrhea hospitalizations due to rotavirus was stable over the 16 year period (Figure 2). The median proportion of children that tested positive for rotavirus did not vary greatly by geographic region (range for North, Central, and Southern regions: 37.7%−47.3%). Thirty-three studies were conducted in urban areas (median rotavirus positive: 39.8%, range: 7.3%−65.6%), and 6 were conducted in rural areas (median rotavirus positive: 46.7%, range: 43.7%−54.3%). For pooled data on cumulative rotavirus hospitalization incidence from 12 studies, 14% of rotavirus gastroenteritis hospitalizations occurred in children aged <6 months, and 91% of rotavirus gastroenteritis hospitalizations occurred by age <24 months (Figure 3) [8, 12–14, 26, 29, 31, 49, 52–55].

In 10 outpatients studies conducted between 1998 and 2013, a total of 16,994 (range per study: 155–10,140) children <5 years of age with acute gastroenteritis were evaluated (Table 2). A median of 30.7% (range: 12.3%−35.4%) of these children tested positive for rotavirus. The proportion of children that tested positive for rotavirus was reported as 27.3%−35.4% in 3 studies conducted Northern China, 30.8% in 1 study conducted in Central China, 12.3%

−30.7% in 5 studies conducted in Southern China, and 31% in one study conducted various locations in Gansu Province. All studies were conducted in urban areas.

Rotavirus strain distribution

We examined rotavirus strain distribution data for the years 1995–2013 from 35 studies that met the inclusion criteria [7, 8, 10–14, 17, 19, 20, 24, 27–29, 32, 35, 38, 45, 47, 52–67] (Figure 4). In 3 studies with data for 1995–1999, G1 was the predominant reported G type, accounting for 70% of strains; data on P types were not available for this time period. In 11 studies with data for 2000–2004, G1 and G3 were the predominant reported G types, accounting for 39% and 38% of strains, respectively. In 8 studies for which P types were reported during the same period, P[8] was predominant, accounting for 59% of strains. In 14 studies with data for 2005–2009, G3 was the predominant reported G type, accounting for 62% of strains, while in 11 studies for the same time period, P[8] was the predominant reported P type, accounting for 60% of strains. In 9 studies with data for 2010–2013, G3 was the predominant reported G type, accounting for 42.3% of strains, while in 8 studies for the same time period, P[8] was the predominant reported P type. No uniform differences in genotype predominance by region were seen within each time period.

DISCUSSION

The findings of this comprehensive, up-to-date literature review affirms that rotavirus is a leading cause of severe diarrheal disease among children in China, causing over 40% of diarrhea hospitalizations and ~30% of diarrhea-related outpatient visits in children aged <5 years. The proportion of diarrhea hospitalizations due to rotavirus was remarkably stable over the 16 year period from 1998 to 2013 and also was similar in different geographic regions and urban/rural settings. Severe rotavirus disease occurs early in life in China with over half of rotavirus-related hospitalizations occurring in the first year of life and 91% of rotavirus related hospitalizations occurring by 2 years of age. However, it is important to note that only 14% of hospitalizations occurred prior to the age of 6 months. Therefore, a vaccination program with doses given early in infancy has the potential to prevent the majority of the burden of severe rotavirus disease. Our review also demonstrates that, while there has been natural, temporal variation in circulating rotavirus strains in China, the predominant local strains are the same as those that are globally dominant [68, 69].

Using estimates of approximately 30 million doses of LLR vaccine distributed since 2000 and a birth cohort of 16 million, the crude national LLR vaccination coverage is only 15.6% with one dose. This may help explain why we observed steady rotavirus positivity rates in our review of the literature even after 2000, the year of vaccine licensure. However, without accurate national and local population coverage data, it is difficult to gauge the true level of impact that LLR vaccine may have had on rotavirus disease trends in China and whether decreases in rotavirus disease in specific areas were due to vaccine use. More scientifically rigorous studies are essential to evaluate the impact and effectiveness of this vaccine.

This review has some limitations. First, due to its retrospective nature, people in studies are not the same. Second, given strict inclusion and exclusion criteria, a greater proportion of the included studies were from urban location, which limits the generalizability of our findings.

Additionally, we were unable to obtain national level data that would have covered more provinces of China, including the poorest areas in western China. Third, we were unable to include all studies identified through the literature searches given different study periods, ages of enrollment, case definitions of severity, and diagnostic assays used. However, by using a uniform set of inclusion criteria, we were able to compare studies over time, across regions, by urban/rural location, and by clinical setting as a marker of disease severity where hospitalizations represent more severe disease. Despite these limitations, we were able to review a large number of studies, and the detection rates observed in this review are similar to those found in the most recent large prospective study in China [70].

The introduction of rotavirus vaccines into routine immunization programs worldwide has resulted in substantial declines in rotavirus-related morbidity and mortality in the countries that have introduced vaccine [6, 71]. The two globally recommended rotavirus vaccines, Rotarix (GlaxoSmithKline, Rixensart, Belgium) and RotaTeq (Merck and Co. Inc, Pennsylvania, USA), have been introduced into over 75 countries worldwide since 2006 and have had good effectiveness against severe rotavirus disease under conditions of routine use and a notable impact in reducing rotavirus hospitalization in many countries 72, 73]. Currently in China, the two globally recommended rotavirus vaccines and a new trivalent lamb-human reassortant rotavirus vaccine are in pre-licensure clinical trials, and several other locally manufactured rotavirus vaccines are in development.

Our findings affirm that rotavirus is the major cause of childhood diarrheal disease in China and suggest that a vaccination program with doses given early in infancy has the potential to prevent the majority of the burden of severe rotavirus disease. This information should help inform future decisions on national rotavirus vaccine introduction in China.

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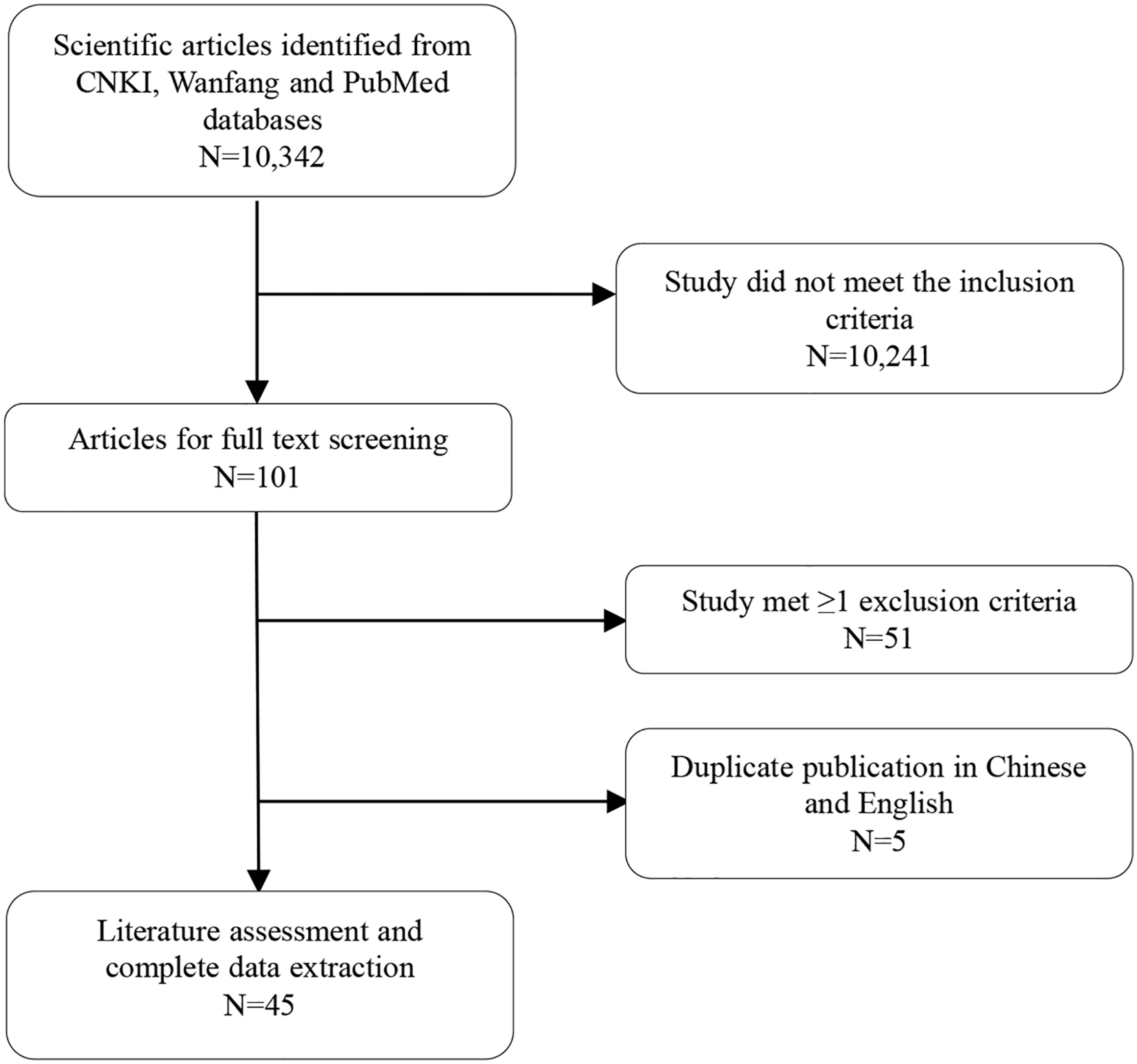

Figure 1.
Eligibility of studies for inclusion in the systematic review

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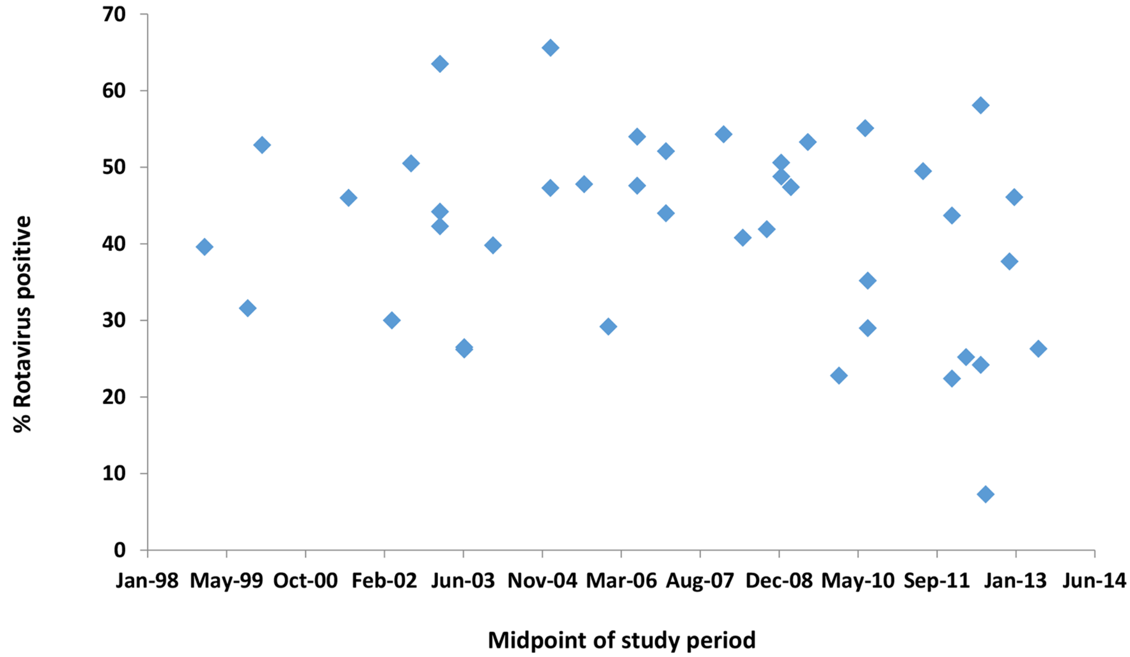

Figure 2.

Rotavirus positivity by study midpoint in children age <5 years hospitalized with acute gastroenteritis, 1998–2013

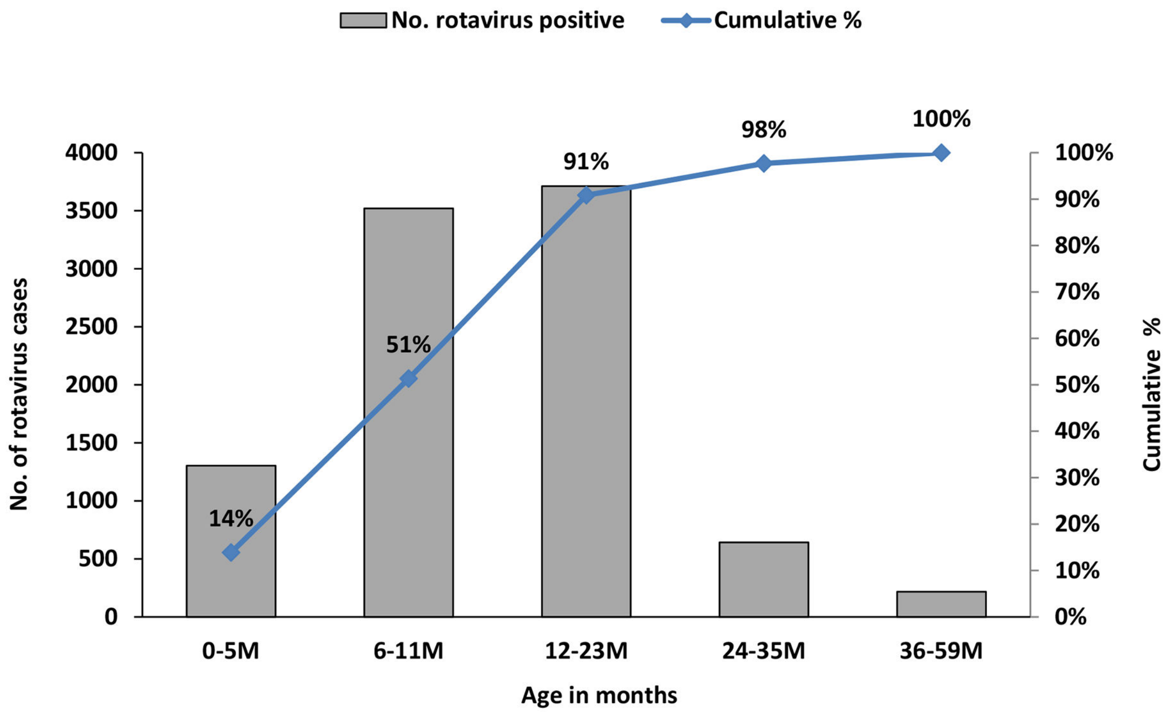

Figure 3.

Age distribution of children hospitalized with acute rotavirus gastroenteritis in China, 1998–2013. Bars denote the number of hospitalizations in different age groups and the line represents the cumulative rotavirus-positive rate.

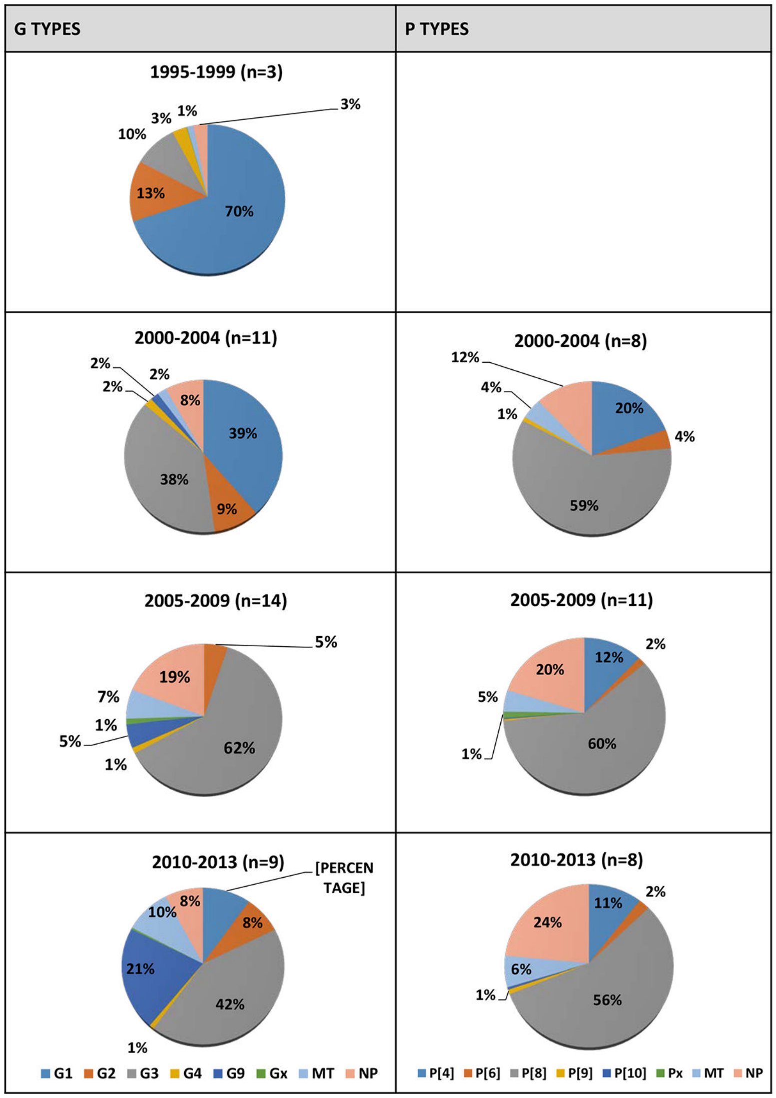

Figure 4.

Distribution of common G and P types in children<5 years old in China, 1995–2013[a]

Table 1.

Rotavirus detection rates for 41 inpatient studies of pediatric diarrhea among children <5 years of age in China, 1998–2013

Location	Study characteristics		Patient characteristics		
	Study period (year/month)	Duration (months)	Number	% rotavirus positive	Reference
Northern China					
Urban					
Beijing	1998/4–2001/3	36	209	31.6	[7]
Beijing	2013/1–2013/12	12	243	26.3	[43]
Changchun	1998/7–2001/6	36	1056	52.9	[8]
Changchun	2001/8–2004/7	36	1227	63.5	[9]
Changchun	2004/7–2005/6	12	400	47.3	[10]
Changchun	2010/1–2010/12	12	460	35.2	[11]
Changchun	2005/1–2013/12	108	3934	53.3	[45]
Changchun	2012/1–2012/12	12	387	58.1	[44]
Hebei	2006/1–2006/12	12	454	47.6	[12]
Lanzhou	2005/1–2007/12	36	544	54.0	[14]
Liaoning	2009/1–2011/12	36	169	29.0	[15]
Chizhou	2005/1–2006/12	24	428	29.2	[33]
Rural					
Lulong	1999/7–2003/6	48	1236	46.0	[16]
Lulong	2001/8–2004/7	36	945	44.2	[9]
Lulong	2007/1–2010/12	48	1643	48.8	[13]
Lulong	2008/9–2009/8	12	426	47.4	[17]
Lulong	2011/1–2012/12	24	741	43.7	[34]
Northern China median (range)			*460 (169–3934)*	*47.3 (26.3–63.5)*	
Central China					
Urban					
Henan	2004/1–2005/12	24	1628	65.6	[18]
Hunan	2009/1–2010/12	24	759	22.8	[19]
Taiyuan	2007/11–2008/10	12	346	40.8	[20]
Taiyuan	2010/1–2012/12	36	989	49.5	[35]
Nanchang	2009/7–2011/6	24	390	55.1	[36]
Anhui	2011/1–2012/12	24	549	22.4	[37]
Anhui	2011/4–2013/3	24	310	25.2	[38]
Central China median (range)			*549 (310–1628)*	*40.8 (22.4–65.6)*	
Southern China					
Urban					
Guangzhou	2002/1–2005/12	48	399	39.8	[21]
Hong Kong	2001/4–2003/3	24	5881	30.0	[22]
Kunming	2001/8–2004/7	36	949	42.3	[9]

Location	Study characteristics		Patient characteristics		Reference
	Study period (year/month)	Duration (months)	Number	% rotavirus positive	
Meizhou	2008/4–2009/3	12	568	41.9	[23]
Shanghai	2001/1–2005/12	60	5534	26.2	[24]
Shanghai	2001/1–2005/12	60	5411	26.5	[25]
Shanghai	2012/2–2013/1	12	619	7.3	[39]
Zhuhai	2008/7–2009/6	12	478	50.6	[26]
Shenzhen	2011/1–2013/12	36	14511	24.2	[41]
Guiyang	2012/1–2013/12	24	1607	37.7	[40]
Rural					
Luocheng	2007/1–2008/12	24	617	54.3	[27]
Southern China median (range)			*949 (399–14,511)*	*37.7 (7.3–54.3)*	
Various locations					
8 cities	1998/1–1999/12	24	1093	39.6	[28]
6 sentinel hospitals	2001/8–2003/7	24	3149	50.5	[29]
11 sentinel hospitals	2003/8–2007/7	48	7846	47.8	[30]
9 cities	2006/1–2007/12	24	3862	44.0	[31]
3 cities	2006/1–2007/12	24	2328	52.1	[32]
2 cities	2012/8–2013/7	12	521	46.1	[42]
Median (range) of all studies			***741 (169–14,511)***	***44 (7.3–65.6)***	

Table 2.

Rotavirus detection rates for 10 outpatient studies of pediatric diarrhea among children <5 years of age in urban China, 1998–2013

Location	Study characteristics		Patient characteristics		Reference
	Study period (year/month)	Duration (months)	Number	% rotavirus positive[a]	
Northern China					
Beijing	1998/4–2001/3	36	275	27.3	[7]
Changchun	1998/7–2001/6	36	155	31.0	[8]
Rizhao	2007/1–2009/12	36	997	35.4	[46][b]
Central China					
Nanchang	2009/7–2011/6	24	234	30.8	[36]
Southern China					
Jinzhou	2003/1–2004/12	24	646	30.7	[48]
Xiamen	2009/1–2011/12	36	2566	30.6	[49]
Shaoxing	2010/1–2012/12	36	10140	12.3	[55]
Guangzhou	2011/6–2013/5	24	709	21.6	[50]
Pinghu	2013/1–2013/12	12	1059	23.6	[51]
Various locations					
2 cities	2012/8–2013/7	12	213	31.0	[42]
Median(range)			***623(155–10,140)***	***30.8(12.3–52.0)***	

[a]Detection by enzyme-linked immunosorbent assay;

[b]included children 60 months of age