Etiology of acute diarrhea in children in Shanghai, 2015-2018

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Abstract

Background Diarrhea is still a major cause of childhood morbidity and mortality worldwide. This hospital-based study aimed to monitor the consecutive epidemiological trend of etiology in children with acute diarrhea in Shanghai.

Methods Outpatient children with diarrhea were prospectively enrolled within 7 days after onset of diarrheal symptoms during 2015-2018. Fresh stool samples were collected for testing enteropathogens. Enteric bacteria were identified and typed through culture and serotyping. Enteric viruses were identified through real-time PCR assay. had

Results Enteric pathogens were identified in 1572 (58.4%) of the 2692 enrolled children with acute diarrhea. Viruses were more frequently detected than bacteria (41.3% versus 25.0%), and co-infection with 2 or more pathogens was found in 13% of outpatients. Nontyphoidal Salmonella spp . (NTS) was the most common bacteria with 10.3% of isolate rate, followed by enteropathogenic Escherichia coli (EPEC) (6.5%), enteroaggregative Escherichia coli (EAEC) (6.2%), Campylobacter spp . (3.6%), enterotoxigenic Escherichia coli (ETEC) (1.1%), Shigella spp . (0.2%), and enterohemorrhagic Escherichia coli (EHEC) (0.1%). Rotavirus was the most common virus with 16.0% of detection rate, followed by norovirus (15.5%), adenovirus (7.2%), sapovirus (3.0%) and astrovirus (2.7%).

Conclusions Infectious diarrhea remains the major cause of diarrhea in children in Shanghai. Rotavirus, norovirus and NTS were the major enteric pathogens responsible for diarrhea in Shanghainese children. Improving uptake of rotavirus vaccine and strengthening prevention of foodborne pathogens will be helpful to reduce the burden of diarrheal diseases in children in Shanghai.

Background

Diarrhea is one of the major health problems in children and is responsible for about 8.6% of child deaths worldwide in 2015 (1–3). With the continuous improvement of sanitary and hygiene conditions and safe water supply, there has been a significant reduction in the death of children caused by diarrhea in China and 3.2% of under-five child deaths was attributable to diarrhea in 2015 (4). China is a developing country with unbalanced regional economic development and medical service. The developing areas are often confronted with inadequate of sanitation facilities, shortage of trained health workers and lack the consciousness of personal hygiene compared with the developed areas, which puts children in developing areas at greater risk of diarrhea than in developed areas (5). Our previous study and one study conducted in Beijing and Henan revealed viral diarrhea was more common than bacterial diarrhea in Shanghai and Beijing; however, dysentery remained the major cause of childhood diarrhea in the rural area of Henan (6).

Given that the etiology and epidemiology of infectious diarrhea vary by time and location, continuous monitoring is necessary and helpful to guide the implementation strategies of prevention and management of diarrhea. Thus, we carried out a consecutive 4-year surveillance of infectious diarrhea in outpatient children in Shanghai, aiming to observe the etiological and epidemiological characteristics of acute diarrhea in children and to provide clinical evidence for policy-makers to develop the effective interventions of preventing childhood diarrhea in China.

Materials And Methods

Case definition and enrollment

This surveillance study was conducted during 2015-2018 in the outpatient setting at the Children's Hospital of Fudan University, the largest tertiary teaching pediatric hospital in Shanghai. Diarrhea is defined as at least three abnormally loose stools in previous 24 hours, and an episode of diarrhea is defined as diarrhea onset beginning after at least 7 diarrhea-free days and ending when diarrhea is not present for 7 days (7). Acute diarrhea was defined as episodes of diarrhea lasting for less than 14 days. Eligible cases were excluded from the study if they had a known chronic cause of diarrheal symptoms or had not adequate stool specimens available for bacteria and virus detection.

Sample collection and Laboratory methods

Fresh stool specimens were collected from the first 5-10 diarrheal cases whose symptoms of diarrhea occurred were presented within 7 days before hospital visits and whose fresh stool amount was adequate for microscope examination and microbiological test. For detection of bacteria, stool samples were collected in the special containers with Cary-Blair transport medium and transported to the microbiological laboratory within 24 hours. For virus, 1mL of stool samples were kept in DMEM (Dulbecco's Modified Eagle Medium) at -4°C for nucleic acid extraction.

All samples were submitted to the reference laboratory of Shanghai Changing District Center for Disease Control and Prevention for microbiological test. The enteropathogens tested in this study include five phenotypes of diarrheagenic *Escherichia coli* (DEC), *nontyphoidal Salmonella spp*. (NTS), *Shigella spp*., *Campylobacter spp*., *pathogenic vibrio spp*., *Yersinia enterocolitica*s *spp*., rotavirus, norovirus Group I and Group II, adenovirus, sapovirus and astrovirus. Bacteria pathogens were identified as described in our previous study (8). Viruses were identified based on multiplex quantitative Real-time PCR using BioPerfectus kits (Jiangsu BioPerfectus Technologies Co., Ltd., Jiangsu, China). Experimental procedures were followed strictly according to the manufacturer's instructions. The Co-infection was defined as infection two or more different pathogens or different subtypes.

Statistical Analysis

Data analysis was performed using Excel (version 2016, Microsoft Corporation).

Results

A total of 2692 children with diarrhea at the acute stage of illness we enrolled in this study. The mean age of enrolled children was 21. 7 (SD) months (median age, 12.7 months) and 61.2% of children were male. The detailed demographic characteristics of cases is shown in Table 1. The majority of enrolled children were younger than 3 years, accounting for84.5%.

Overall, enteropathogens were detected in 1572 (58.4%) of 2692 enrolled cases. Rotavirus and norovirus were the most frequently identified viruses with the detection rates being 16.0% and 15.5%, respectively. Ninety-seven percent of Norovirus belonged to GII. Adenovirus was relatively common with the detection rate of 7.2%. However, in 2018, the prevalence of rotavirus and norovirus declined with the increasing prevalence of adenovirus.

NTS was the most common bacteria with 10.3% of isolate rate, followed by enteropathogenic *Escherichia coli* (EPEC) (6.5%), enteroaggregative *Escherichia coli* (EAEC) (6.2%), *Campylobacter spp*. (3.6%), enterotoxigenic *Escherichia coli* (ETEC) (1.1%), *Shigella spp*. (0.2%), and enterohemorrhagic *Escherichia coli* (EHEC) (0.1%). NTS isolates included 37serovars with serovars. *S*. typhimurium and *S*. enteritidis accounting for 39.0% and 25.3%, C*ampylobacter* isolates included *C. jejuni* (96.9%) and *C. coli (3.1%)*, and *Shigella* isolates were all *S*. sonnei. None of *Yersinia enterocolitica, Aeromonas* spp. *Vibrio* spp. and enteroinvasive *Escherichia coli* (EIEC) isolates was identified.

As shown in table 3, enteropathogens were detected more frequently in children aged ≥12 months than in infants except rotavirus which was far less commonly detected in children aged ≥60 months. Enteric viruses were detected more frequently in children aged 12-<36months and 36-<60months (P), however, norovirus was also detected more frequently in children aged ≥60 months. NTS and DEC were detected more frequently in children aged 12-<36months and 36-<60months (P)while *Campylobacter* was detected more frequently in children aged 36-<60months and ≥60 months (P).

The prevalence of enteric viruses usually peaked in autumn and winter but the seasonality of adenovirus was not apparent (Figure 1). The peak season of norovirus usually appeared from August to November, prior to the peak season of rotavirus which appeared from November to February. The prevalence of enteric bacteria usually peaked in summer and autumn (Figure 2).

Discussion

This 4-year surveillance study showed that enteropathogen infections remain the major cause of diarrhea in Shanghainese children and could be responsible for 58.4% of outpatient visits due to diarrhea episodes. The overall detection rate of enteropathogens in Shanghai was higher than the national average level (44.6%) based on the pooled data from 92 surveillance network laboratories (9), which is possibly correlated with the variation of detection capacity by laboratories. However, the prevalence of enteropathogens was lower than that in Vietnam, where 75.2% of diarrheal episodes in outpatient children were potentially attributable to infectious diarrhea and rotavirus and norovirus were more frequently detected than in Shanghai (10). Although the overall detection rate of enteropathogens was similar to that in Salt Lake City of the United Sates (52%), we also noticed the difference in the etiological spectrum, for example, lower prevalence of rotavirus and NTS and higher prevalence of Clostridium difficile were observed, which was not included into our target pathogen tested (11). Our finding showed that rotavirus, norovirus and NTS were the major etiological agents responsible for diarrhea annually in Shanghainese children, which should be the priority targets for intervention.

WHO recommended rotavirus vaccine as the priority vaccine included the national immunization program in 2008 based on the global disease burden of rotavirus diarrhea (12). With the widely introduction of rotavirus vaccination at the global level, the disease burden incurred by of rotavirus-associated diarrhea has reduced remarkably in countries with rotavirus vaccination including national immunization program (13). Although monovalent lamb-derived G10P[15] rotavirus vaccine has been used in China since 2001, the coverage of vaccination is quite low, rotavirus remains the leading cause of diarrhea in Chinese children (14). Pentavalent rotavirus vaccine was introduced in China in 2018. It is worthy of attention to monitor the changing trend of rotavirus diarrhea with the increased demand and uptake of new rotavirus vaccine among infants in China.

The prevalence of norovirus was almost similar to the prevalence of rotavirus in this study and the high activities of sporadic norovirus diarrhea usually occurred earlier than that of rotavirus diarrhea in Shanghai. Norovirus has replaced rotavirus as the leading cause of pediatric gastroenteritis requiring medical attention in countries with a successful implementation of rotavirus vaccination, such as in the US and Nicaragua (15–17). Considering the public health effect of norovirus gastroenteritis in the community and outbreak settings, candidate norovirus vaccines are under development (18). Thus, monitoring the changing trend of norovirus activity is important to predict the potential emerging new GII.4 variants and recombinants, which could result in epidemics and sometimes global pandemics of acute gastroenteritis (21). In addition, adenovirus, sapovirus and astrovirus accounted for 12.9% of diarrhea in outpatient children. These viruses are sometimes associated with outbreaks in semi-closed communities in all age groups, thus, dynamic surveillance of activities of these three viruses is also clinically important (19, 20).We also noticed the detection rates of adenovirus and astrovirus increased in 2017–2018 compared to 2015–2016. It is worthy of attention to whether the shift of prevalent serotypes was associated with increased activities of adenovirus and astrovirus (21–24).

In this study, NTS was the third common pathogen causing 10.3% of diarrhea and was the leading bacterial pathogen in outpatient children with diarrhea. Globally, NTS is an important pathogen of sporadic and outbreak foodborne gastroenteritis and children < 5 years are most susceptible, especially in developed countries (25, 26). The annual prevalence of NTS during 2015–2018 was stable with S. typhimurium and S. enteritidis serovars remaining predominant. Our latest study suggested the transmission sources of S. typhimurium and S. enteritidis in Shanghainese children were diverse, which imposes difficulty to control and prevent NTS infections in Shanghai (27). Currently, the priority strategy of controlling NTS diarrhea is strengthening food safety, which has reduced the incidence of NTS foodborne diseases in the US and in some European countries (28, 29). Campylobacter infection is gradually increasing in recent years in both developing and developed countries (30). C. jejuni is responsible for about 13% of diarrhea in children under five years old in Poland and Campylobacter infection was the most common foodborne pathogen in 2017 in the US (31). However, the prevalence of Campylobacter infection was much lower than the prevalence of NTS infection in Shanghainese children with diarrhea. Campylobacter infection is usually linked with exposure to chicken and its products (32). Since 2013 China government started strengthening the management of live chicken to prevent the transmission of avian influenza, which indirectly reduced the transmission sauce of Campylobacter infection. Urbanization and improvement of water supplies, sanitation, and hygiene have resulted in a remarkable decrease in shigellosis in China since the late 1990s (33). The prevalence of shigella is very low in Shanghai.

DEC was detected in 12.7% of children with acute diarrhea in the study and most DEC isolates were EAEC and EPEC, which is consistent with studies conducted in Israel (34). However, our previous case-control study conducted in 2014 didn't demonstrate the pathogenic significance of EAEC and EPEC (8). Therefore, we are uncertain the role of EAEC and EPEC as an etiological agent of infectious diarrhea in Shanghainese children. Despite ETEC is a common pathogen causing adult diarrhea in shanghai (35), ETEC was not a common pathogen in children with diarrhea. EHEC was also a rare pathogen.

In conclusion, infectious diarrhea remains a major cause of diarrheal illnesses in Shanghainese children. The disease burden of diarrheal illnesses will be promisingly reduced with increased coverage of rotavirus vaccines in susceptible infants and strengthened intervention of foodborne illnesses in Shanghai and China. The findings of this study are useful for public health policy-makers to formulate the effective strategy of controlling and preventing childhood diarrhea in China.

Abbreviations

NTS: *Nontyphoidal Salmonella spp.*; DEC: diarrheagenic Escherichia *coli*; EPEC: enteropathogenic *Escherichia coli*; EAEC: enteroaggregative *Escherichia coli*; ETEC: enterotoxigenic *Escherichia coli*; EHEC: enterohemorrhagic *Escherichia coli*

Declarations

Funding

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HC, XX and MZ conceived and designed the study. HC, ZW, CW, YQ contributed to the collection of samples and clinical data. JG, ZH and XX contributed to the laboratory test and analysis. HC and MZ performed the statistical analysis and drafted the manuscript. MZ reviewed and revised the manuscript. XX reviewed the manuscript and supervised the laboratory data.

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Not applicable.

Ethics approval and consent to participate

This study was approved by the medical ethics Committee of Children's Hospital of Fudan University (No.2014-019). As children enrolled in the study were anonymous and this study did not take interventions on diagnosis and treatment, we just got the verbal consent from parents or guardians before samples were collected.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Demographic characteristics of children with acute diarrhea in Shanghai from 2015 to 2018 [n (%)]

	2015(n=790)	2016(n=605)	2017(n=633)	2018(n=664)	Total (n=2692)
Male	481(60.9)	369(61.0)	388(61.3)	410(61.7)	1648(61.2)
Female	309(39.1)	236(39.0)	245(38.7)	254(38.3)	1044(38.8)
Age (month)					
0-<12	396(50.1)	294(48.6)	292(46.1)	245(36.9)	1227(45.6)
12-<36	287(36.3)	224(37.0)	246(38.9)	289(43.5)	1046(38.9)
36-<60	54(6.8)	45(7.4)	47(7.4)	57(8.6)	203(7.5)
≥60	53(6.7)	42(6.9)	48(7.6)	73(11.0)	216(8.0)

Table 2 The distribution of enteric pathogens in Shanghainese children with diarrhea from 2015 to 2018 [n (%)]

		2015 (n=790)	2016 (n=605)	2017 (n=633)	2018(n=664)	Total (n=2692)
Rotavirus		142(18.0)	105(17.4)	107(16.9)	77 (11.6)	431(16.0)
Norovirus		137(17.3)	103(17.0)	98(15.5)	80 (12.0)	418(15.5)
	GI	5(0.6)	3(0.5)	1(0.2)	3 (0.4)	12 (0.4)
	GII	132(16.7)	100(16.5)	97(15.3)	77 (11.6)	406 (15.1)
Adenovirus		47(5.9)	33(5.5)	51(8.1)	62 (9.3)	193 (7.2)
Sapovirus		31(3.9)	13(2.1)	17 (2.7)	19 (2.9)	80(3.0)
Astrovirus		12(1.5)	8(1.3)	26 (4.1)	27 (4.1)	73(2.7)
diarrheagenic *Escherichia coli*		76(9.6)	72(11.9)	90(14.2)	104(15.7)	342(12.7)
	EAEC	38(4.8)	38(6.3)	52(8.2)	40 (6.0)	168(6.2)
	EPEC	39(4.9)	37(6.1)	37(5.8)	63(9.5)	176(6.5)
	ETEC	8(1.0)	9(1.5)	6(0.9)	7(1.1)	30(1.1)
	EHEC	0(0)	0(0)	2(0.3)	1(0.1)	3(0.1)
nontyphoidal Salmonella		67(8.5)	63(10.4)	62(9.8)	85(12.8)	277(10.3)
Shigella		4(0.5)	1(0.2)	0(0)	0(0)	5(0.2)
Campylobacter		44(5.6)	15(2.5)	15(2.4)	23(3.5)	97(3.6)

Table 3 The detection rate of enteric pathogens in different age groups [n (%)]

	0-<12 months (n=1227)	12-<36 months (n=1046)	36-<60 months (n=203)	≥60 months (n=216)	P value
Rotavirus	168(13.7)	217(20.7)	31(15.3)	15(6.9)	
Norovirus	151(12.3)	202(19.3)	30(14.8)	35(16.2)	
Adenovirus	62(5.1)	97(9.3)	22(10.8)	12(5.6)	
Sapovirus	17(1.4)	49(4.7)	8(3.9)	6(2.8)	
Astrovirus	24(2.0)	37(3.5)	6(3.0)	7(3.2)	
diarrheagenic *Escherichia coli*	113(9.2)	177(16.9)	28(13.8)	24(11.1)	
nontyphoidal Salmonella	84(6.8)	139(13.3)	34(16.7)	20(9.3)	
Shigella	0(0)	2(0.2)	1(0.5)	2(0.9)	
Campylobacter	13(1.1)	48(4.6)	18(8.9)	18(8.3)	

Figures

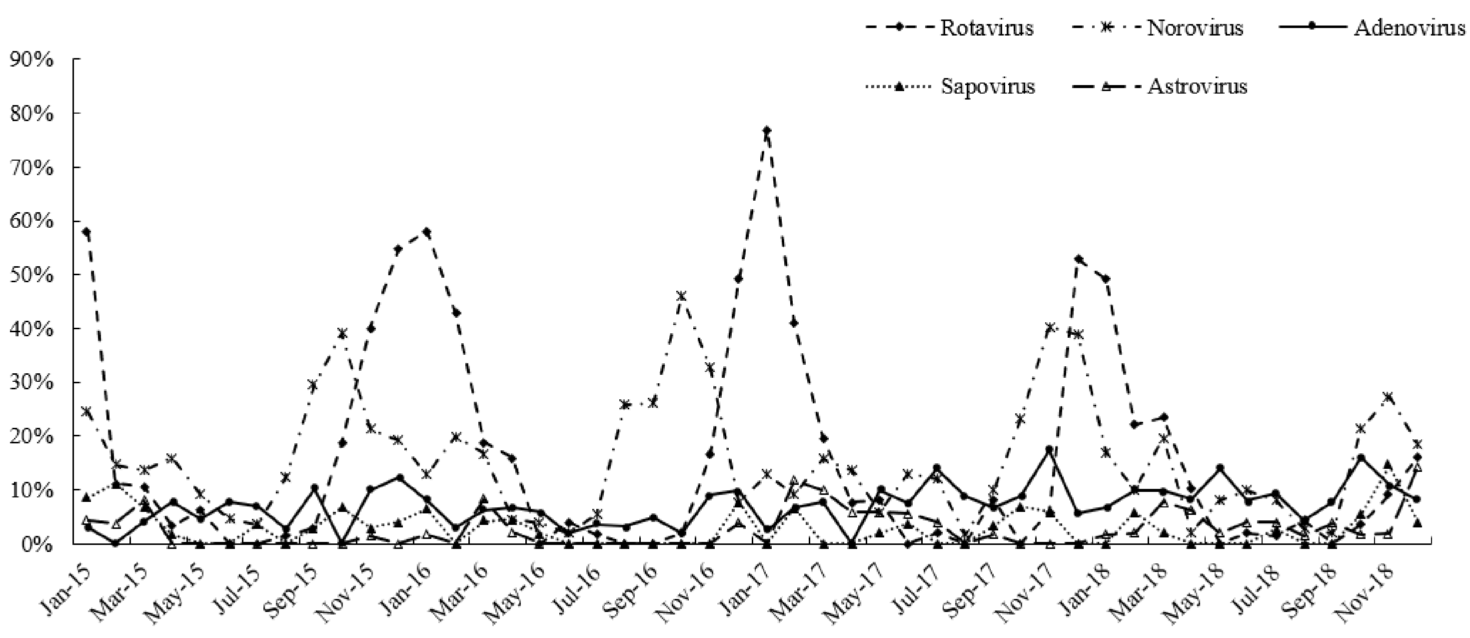

Figure 1

Seasonal prevalence of virus in children with acute diarrhea in Shanghai

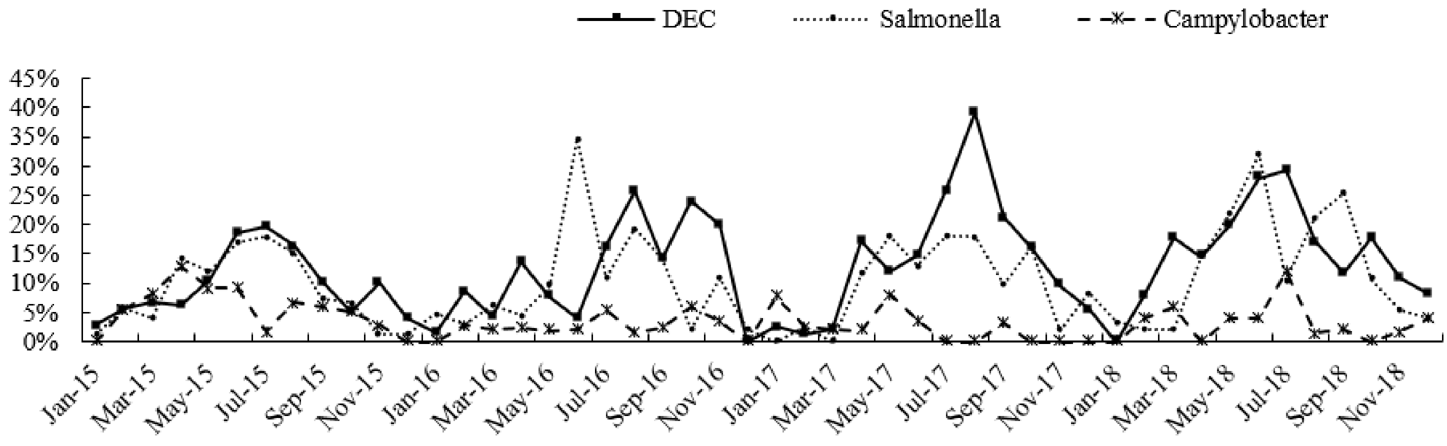

Figure 2

Seasonal prevalence of bacteria in children with acute diarrhea in Shanghai