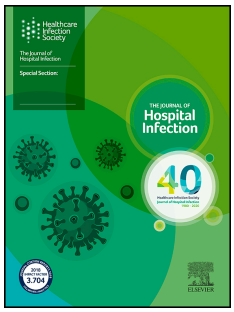

Norovirus Outbreaks in Hospitals in China: A Systematic Review

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Summary

Background: Norovirus (NoV) outbreaks in hospitals can potentially impair patient care and result in significant financial expenses. There is currently limited information on hospital NoV outbreaks in the Chinese mainland.

Aim: To systematically review the published literature to describe the characteristics of NoV outbreaks in Chinese mainland hospitals to facilitate prompt identification and control of outbreaks.

Methods: According to the Preferred Reporting Items for Systematic Review and Meta-Analysis standards, this systematic review was carried out. Databases including PubMed and Web Of Science and Chinese Journals Online databases (China National Knowledge Infrastructure (CNKI), Chinese Wan Fang digital database (WANFANG) were searched from inception to July18, 2022.

Findings: A total of 41 NoV Chinese hospital outbreaks occurring before July18, 2022 were reported in 32 articles. Most reported outbreaks were from Shanghai and Beijing, and occurred in December and January. Cases were mainly adults. The male-to-female ratio was 1.22:1. The majority of cases in NoV outbreaks were hospitalized patients (56.82%); medical staff were affected in 15 outbreaks. NoV outbreaks occurred in both private and public hospitals, and in secondary and tertiary care centres), and occurred mainly in internal medicine and geriatric departments. Person-to-person transmission was the primary transmission mode and GII was more prevalent.

Conclusion: NoV outbreaks in hospitals can affect both patients and healthcare workers, sometimes causing serious financial losses. In order to have a more complete understanding of the disease burden caused by norovirus outbreaks, surveillance need be established in hospitals.

Introduction

Norovirus (NoV) is an important cause of gastroenteritis in healthcare settings; these infections occur frequently, are highly contagious, and also are difficult to control(1). NoV infection is increasingly being recognized as a major threat for the hospital that can affect both patients and healthcare workers(2). For example, one NoV outbreak report affected 143 patients and 30 healthcare workers, restricted new admissions to affected units, and resulted in 1,192 lost bed-days(3). Hospital NoV outbreaks can lead to disruption of patient care and substantial economic costs associated with containment and ward closure(4). The economic impact of an NoV outbreak in a US hospital in 2004 was estimated to be over US$650,000 (5). Hospital outbreaks of acute gastroenteritis were estimated to cost £115 million in England in 2002-2003(6). Thus, there are surveillance systems for NoV outbreaks in hospital, such as the English hospital NoV outbreak reporting system (HNORS)(7). Despite the importance of NoV in hospitals, mainland Chinese data on hospital NoV infections and outbreaks are limited, and there is no national surveillance system. To understand the characteristics of NoV outbreaks in hospitals in Chinese mainland, and provide evidence for timely management and effective control of NoV outbreaks in hospitals, we analyzed the epidemiological characteristics of NoV outbreaks in hospitals that published before July18, 2022.

Methods

Information sources and search strategy

This systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) standards. PubMed, Web of Science and Chinese Journals Online databases (China National Knowledge Infrastructure (CNKI), Chinese Wan Fang digital database (WANFANG) were searched from database inception to July18, 2022.

PubMed and Web of Science were searched using medical subject heading (MeSH) terms in all fields including: “norovirus” AND “outbreaks” AND “hospitals”). Chinese databases were searched using corresponding Chinese terms in the title, abstract and keywords, including: norovirus/norwalk, outbreak/epidemic/clustered, hospital/ nosocomial/ward to select the Chinese studies.

Outbreak definition

Norovirus outbreak: 2 or more epidemiologically linked cases of acute gastroenteritis in the same setting, of which at least 2 cases tested positive for norovirus.

Suspected norovirus outbreak: 2 or more epidemiologically linked cases of acute gastroenteritis in the same setting, of which one case tested positive for norovirus.

Inclusion and exclusion criteria

Studies had to meet all four of the following criteria for inclusion (i) reported NoV outbreaks occurred in Chinese mainland, and published in English or Chinese; (ii) measurable outcomes such as outbreak duration, number of cases, NoV genotype and transmission routes; (iii) positive tests for NoV in stool or vomit specimens of patients; (iv) outbreaks occurred in hospitals.

We excluded studies if they (i) did not meet the definition of a NoV outbreak or suspected NoV outbreak; (ii) reported outbreaks were caused by other pathogens in addition to NoV; (iii) were not available as full-text articles; (iv) were written in languages other than English or Chinese; (v) were review articles.

Data abstraction

Two independent reviewers (Fan Yu and Jiamei Fu) screened titles and abstracts for relevance. They used a standardized approach to conduct the literature search, data extraction. Any disagreements were resolved through discussion with a third reviewer. The reasons for exclusion were documented.

Statistical analysis

We used Endnote X9 (Clarivate Analytics, https://endnote.com) to import and manage retrieved records, Excel 2019 to collect epidemiological information of norovirus outbreaks and plot bar graphs. Statistical analysis was performed using Statistical Product Service Solutions software (version 19.0, International Business Machines Corporation, Chicago, IL, USA).

We used Pearson Chi-Square to compare the incidence of clinical features (diarrhoea, vomiting, fever, abdominal pain, nausea). Multiple comparison was performed by the

Bonferroni method. The statistical significance was set at a two-sided p-value of 0.05.

Results

Selection of studies

A total of 2544 publications were identified from the database search, after removing repeated records, 2035 literature was screening by title and abstract; 5 of these articles were included from citation searching. We assessed 70 full-text articles for eligibility. Of these, 15 articles reported repeated outbreaks, 9 did not have enough information for analysis, 7 did not have information of outbreaks, 8 reported the outbreaks outside Chinese mainland, and 4 did not occur in hospital. A total of 41 NoV outbreaks reported in 32 articles were finally included (Figure 1).

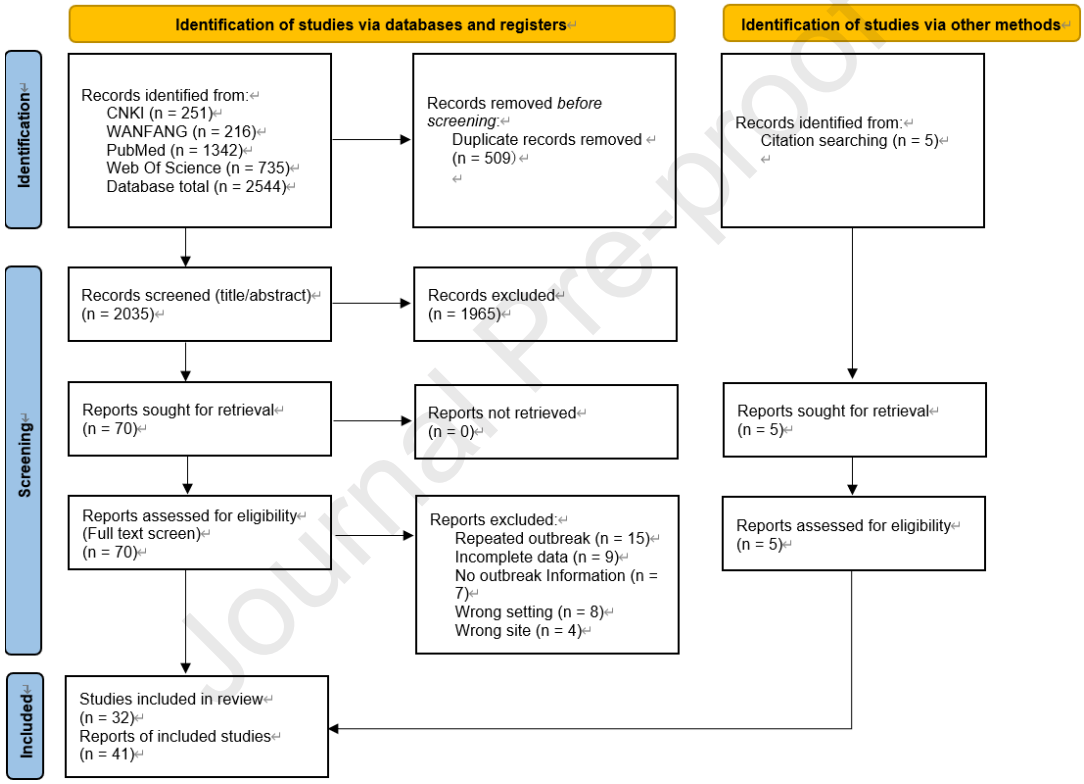

Figure 1. PRISMA flow diagram for the selection of studies(8).

Overview of the outbreaks

A total of 41 NoV outbreaks, amounting to 1231 cases, were reported in Chinese hospitals before July18, 2022. Three of these outbreaks were suspected NoV outbreaks. The largest outbreak involved 406 cases and the smallest 5 cases; the median number of cases was 18. 40 studies reported the outbreak duration; the median was 7 d (range 2 to 27 d). Numbers of persons exposed and attack rates were reported for 35 outbreaks. The number of persons exposed ranged from 10 to 3,766; the median attack rate was 16.70% (range 3.13% to 100%).

The main characteristics of individual outbreak included in the systematic review are summarized in Table 1. Most outbreaks were attributed to person-to-person transmission, but

much the largest outbreak (406 cases, affecting 7 buildings) was due to contamination of water supply system(32).

Table 1

Characteristics of included norovirus outbreaks

Year of publication	Provinces/ municipalities	Year	Month	Duration (d)	No. exposure	No. cases	Attack rate (%)	Genotype	Modes of transmission	References
2007	Beijing	2006	12	2	36	8	22.22%	NA	unknown	(9)
2007	Beijing	2006	11	13	NA	18	NA	NA	person-to-person	(10)
2007	Zhejiang	2006	12	19	71	18	25.35%	GII	person-to-person	(11)
2007	Zhejiang	2007	12	26	NA	22	NA	NA	unknown	(12)
2008	Guangdong	2006	12	23	1500	47	3.13%	NA	person-to-person	(13)
2008	Beijing	2006	11	4	NA	8	NA	NA	NA	(14)
2008	Beijing	2006	11	27	1412	87	6.16%	NA	person-to-person	(15)
2008	Beijing	2006	12	10	NA	8	NA	GII	NA	(16)
2008	Guangdong	2007	1	5	68	14	20.59%	NA	unknown	(17)
2009	Beijing	2006	10	3	NA	7	NA	NA	person-to-person	(18)
2009	Beijing	2008	3	7	78	13	16.67%	NA	NA	(19)
2009	Beijing	2006	7	3	55	8	14.55%	NA	person-to-person	(20)
2009	Beijing	2008	2	3	52	9	17.31%	NA	person-to-person	(21)
2011	Beijing	2007	10	13	NA	24	NA	GII.4	person-to-person	(22)
2012	Beijing	2010	1	4	40	5	12.50%	NA	person-to-person	(23)
2012	Shanghai	2010	12	8	10	10	100.00 %	NA	NA	(24)
2012	Guangdong	2011	6	6	69	10	14.40%	NA	person-to-person	(25)
2013	Guangxi	2012	7	9	92	22	23.91%	GII	person-to-person	(26)
2014	Beijing	2013	1	5	70	18	25.71%	GII	multiple	(27)
2015	Beijing	2010	12	7	135	22	16.30%	NA	person-to-person	(28)
2015	Shanghai	2013	4	16	147	17	11.56%	GII	person-to-person	(29)
2015	Anhui	2013	12	5	130	17	13.08%	GII	multiple	(30)
2015	Tianjing	2014	12	9	144	28	19.44%	NA	person-to-person	(31)
2016	Jiangsu	2012	7	7	3766	406	9.64%	GI	waterborne	(32)
2016	Guangdong	2015	1	6	207	34	16.43%	NA	unknown	(33)
2016	Zhejiang	2015	1	5	57	16	28.07%	GII	person-to-person	(34)

2016	Beijing	2013-2015	NA	NA	15	9	60.00%	GII	person-to-person	(35)
2017	Shanghai	2014	12	12	400	34	8.50%	GII.17	person-to-person	(36)
2018	Shanghai	2008	3	7	74	18	24.32%	NA	person-to-person	(37)
2018	Shanghai	2008	12	5	73	8	10.96%	GII	person-to-person	(37)
2018	Shanghai	2012	1	8	111	22	19.82%	GII	person-to-person	(37)
2018	Shanghai	2012	2	3	121	10	8.26%	GII	person-to-person	(37)
2018	Shanghai	2012	12	11	108	23	21.30%	GII	person-to-person	(37)
2018	Shanghai	2013	3	8	71	13	18.31%	GII	person-to-person	(37)
2018	Shanghai	2015	2	4	62	13	20.97%	GII	person-to-person	(37)
2018	Shanghai	2015	3	8	94	15	15.96%	GII	person-to-person	(37)
2018	Shanghai	2016	3	9	147	22	14.97%	GII	person-to-person	(37)
2018	Shanghai	2017	4	6	97	16	16.49%	GII	person-to-person	(37)
2019	Shandong	2016	2	5	394	40	42.10%	GII	multiple	(38)
2020	Shaanxi	2019	3	7	79	22	27.85%	GII	person-to-person	(39)
2020	Shanghai	2018	11	7	259	27	10.42%	GII.6	NA	(40)

Epidemiological characteristics of outbreaks

NoV hospital outbreaks were reported almost every year, with the greatest number of reports (10) in 2006 (Figure 2). The average time interval between occurrence of the 39 outbreaks for which exact times were reported and publication was 33 months. Outbreaks occurred mainly in December (30.00%, 12/40), January and March (15.00%, 6/40) (Figure 3).

Fourteen NoV hospital outbreaks were reported in Shanghai and 14 in Beijing, followed by 4 in Guangdong and 3 in Zhejiang respectively. There was only 1 NoV hospital outbreak in Anhui, Jiangsu, Shandong, Shaanxi, Tianjin and Guangxi. Among 14 NoV hospital outbreaks in Shanghai, 10 out of 14 occurred in Xuhui district. A total of 13 outbreaks occurred in Beijing, with 4 in Haidian, 3 each in Chaoyang, Dongcheng and Xicheng Districts (Table I). The great majority of outbreaks were attributed to

The NoV genotype was reported in 23 outbreaks; 22 were caused by GII and one was caused by GI.

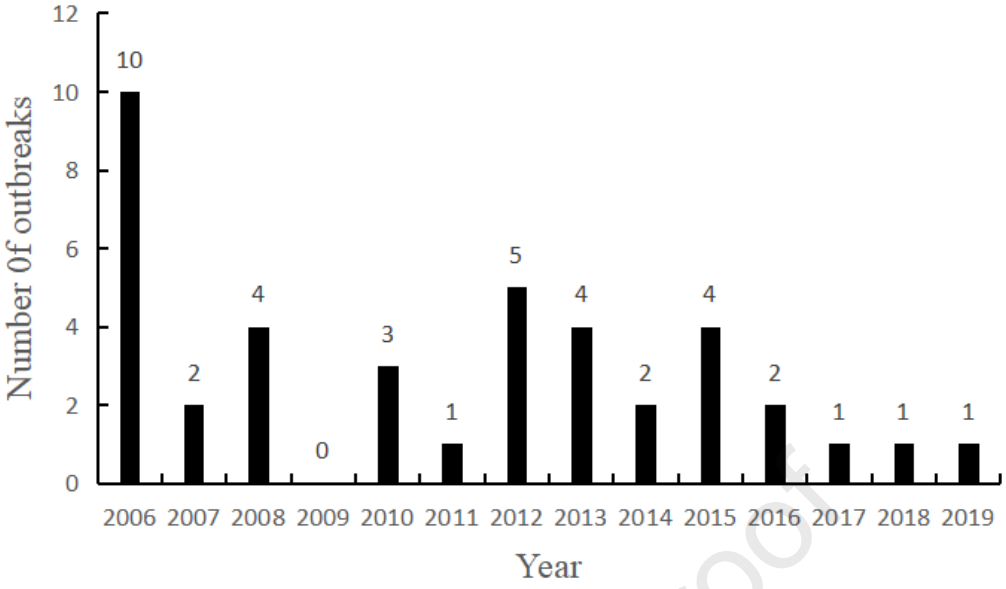

Figure 2. Yearly distribution of 40 hospital norovirus outbreaks in 10 regions.

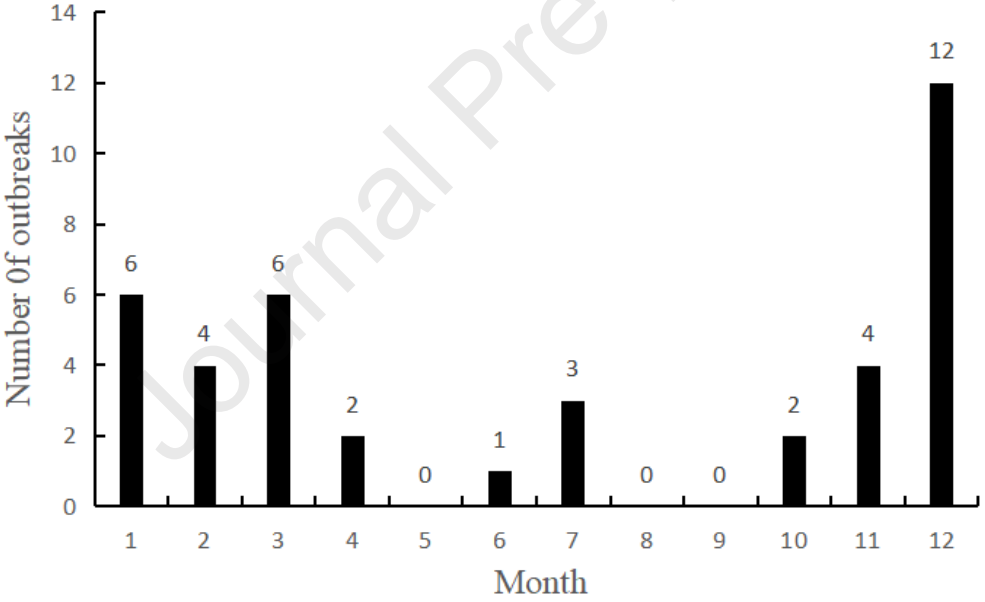

Figure 3. Monthly distribution of 40 hospital norovirus outbreaks in 10 regions.

Characteristics of cases

The ages of cases were described in 23 outbreaks. Ages ranged from 1.5 to 100 years; most cases were adults. There was much difference in the age ranges in outbreaks. Minimum age ranged from 1.5 to 75 years, and maximum ages from 63 to 100 years. Gender information was available for 20 outbreaks involving 486 cases. 267 cases were male and 219 were female (male-to-female ratio 1.22:1). The majority of infected individuals in the 24 outbreaks where the status of cases was noted were hospital inpatients, accounting for 56.82% (521/917) (Table II). However most of the outbreaks (15/24, 62.50%) also involved medical staff.

The symptoms associated with NoV infections are shown in Table II. Diarrhoea was much the commonest symptom, occurring in 85.96% of cases ($P < 0.05$, $\chi^2 = 818.514$). Multiple comparisons of symptoms showed that diarrhoea was significantly commoner than vomiting, abdominal pain and nausea, which were significantly more common than fever ($P < 0.005$).

Table II. Case characteristics of hospital NoV outbreaks.

Characteristics	% (n/N)
Sex	
Male	54.94% (267/486)
Female	45.06% (219/486)
Occupation	
Hospitalized patients	56.82% (521/917)
Medical staff	28.68% (263/917)
Other persons	14.50% (133/917)
Clinical features	
Diarrhoea	85.96% (802/933)
Vomiting	44.07% (405/919)
Fever	18.16% (144/793)
Abdominal pain	47.89% (374/781)
Nausea	49.43% (305 /617)

*Data on case: sex were included in 20 (45.45%), occupation in 24 (57.50%), and Clinical features (diarrhoea, vomiting, fever, abdominal pain, nausea) in 25， 23, 18, 14, 12 outbreaks separately.

Types of hospitals

Forty NoV outbreaks occurred in hospitals and 1 in acommunity health service centre. The types of hospitals were reported in 29 outbreaks, 13 occurred in tertiary hospitals (6 in grade A tertiary hospitals), 5 in secondary hospitals, 5 in primary hospitals, 4 in specialized hospitals and 1 each in provincial and general hospitals. The affected departments were identified in 31 outbreaks. Most outbreaks occurred in internal medicine (58.06%, 18/31) and geriatric (38.71%, 12/31) departments. There was one outbreak affecting six departments: neurosurgery, respiratory, orthopaedic, dermatology, cardiology and traditional surgery department.

Laboratory findings

Sample types were recorded for 410 samples in 28 outbreaks. NoV detection rates were 51.98% (131/252) in faeces, 46.10% (65/141) on anal swabs and 37.50% (3/8) in faeces.

Virological testing of environmental samples was performed in 13 outbreaks, and was positive in 9. Positive sites were a male toilet, beds. countertops, waste bins, flush toilets and

cleaning equipment (mops, cloths). Staff hand sampling was undertaken in 8 outbreaks with NoV detected on staff hands in one outbreak,

Control measures

Control measures were described in 33 outbreaks and were basically isolating the source of infection, cutting off the transmission route and health education. The key priorities were isolating patients and cleaning the surroundings. Cases were isolated in 31 outbreaks: bedspace isolation was used in 11, a specialised isolation ward was established in 5 outbreaks, toilet isolation only was employed in 1 outbreak, staff segregation in 2 outbreaks (sick nurses caring for sick patients), and case movement was restricted in 1 outbreak. Ward closure was only employed in 4 outbreaks, the duration of closer being 3, 5 and 7 days where this was specified.

Specific disinfection measures were recorded in 23 outbreaks. In ten outbreaks chlorinated disinfectants were used, with six specifying concentration of disinfectant used (usually 1000 ppm).

Discussion

In China, NoV acute gastroenteritis outbreaks are primarily reported through “National Public Health Emergency Event Surveillance System (PHEESS)” and “CaliciNet China”, but these two systems do not accurately describe the burden of NoV outbreaks in Chinese hospitals. Studies showed data from PHEES and CaliciNet China only showed 4 and 3 NoV outbreaks in hospital, respectively separately (41, 42). In this study, we focused on 41 hospital outbreaks of NoV reported before July18, 2022. The studies showed a pronounced seasonal distribution. Person-to-person transmission was the predominant mode of transmission and the prevalent norovirus was GII. It was noteworthy that more developed region such as Shanghai and Beijing reported more outbreaks, which accords with our earlier observation(43) that more developed areas reported more NoV outbreaks.

Our data showed older adults are more likely to acquire a hospital NoV infection. Most likely, this is caused by longer hospital stays of the elderly and therefore extended exposure. However, increased susceptibility to NoV of the elderly and chronically ill may also be a factor (44). In our analysis, there was more NoV cases in males than females. However, in another study, women constituted 61% (n = 1592) of patients aged ≥70 years(44, 45).

NoV outbreaks mainly affected inpatients, but medical staff were also affected in most reported outbreaks. However, medical staff can also be the main affected population in some NoV outbreaks (5).It is possible that numbers of healthcare workers are understated because infections are not reported, especially if symptoms occur over weekends or during holidays(46).

The main finding of this review is that nosocomial NoV outbreaks cause morbidity of both staff and patients, as well as leading to high financial costs to institutions. Ministry of

Health, the People's Republic of China (National Health Commission of the People's Republic of China) issued the "The Measures for the Administration of the Hospital Grade (Trial Draft)" in 1989. Hospitals at primary, secondary and tertiary levels are assessed and identified as A, B and C in accordance with the measures, with an additional special grade for tertiary hospitals, for a total of three levels and ten grades (47). Almost half of NoV hospital outbreaks (44.83%,13/29) occurred in tertiary hospitals, with 6 in Grade A tertiary hospitals. This may be attributed to better hospital infection reporting systems and higher professionalism of health care staff. NoV hospital outbreaks mainly occurred in internal medicine departments and geriatric departments. Wolak Z et al. found that more gastrointestinal infections were reported in internal medicine wards, which accounted for 21.4% (48). These services may have longer hospital stays, especially among older adults (4), this may patients' chances of being involved in a NoV outbreak. NoV nosocomial outbreaks primarily affect weaker groups, such as elderly people living in institutions and people with impaired immune systems(49).

Control measures should be in place during outbreaks, including hand washing and isolation of infected residents, exclusion of symptomatic staff and visitors, environmental disinfection, and management of contaminated waste and laundry. However, in the majority of reports from China, only bedspace, rather than single room, isolation was employed. Although chlorine-based disinfection was widely used, varying concentrations were used. As there were no standard guidelines for the prevention and management of NoV outbreaks in China in the early years, hospitals in China were unable to take effective infection control measures. The Chinese Center for Disease Control and Prevention released "Guidelines on Outbreak Investigation, Prevention and Control of Norovirus Infection (2015)", which specified the methods of disinfection of norovirus. Patients' vomit and feces should be disinfected with a chlorine solution of 5000mg/L to 10000mg/L, floors, walls and surfaces should be disinfected with a chlorine solution of 1000mg/L, clothing, bedding and other fabrics should be disinfected in a chlorine solution with an effective chlorine of 500mg/L for 30 minutes and then washed(50).

Our analysis has several limitations inherent to published studies. Firstly, our database was collected from outbreaks in studies published online, which is not enough for providing a comprehensive picture of hospital NoV infection in China. Secondly, Information about the genotypes of the isolated strains from each outbreak was not available and it was not possible to evaluate the distribution and effect of the genotype.

Conclusion

Prior to 2022, we identified 41 reported hospital NoV outbreaks in the Chinese mainland. Review of these showed that, as in other countries, outbreaks affect both patients and staff, and can be disruptive and expensive. In order to have a more complete understanding of the disease burden caused by norovirus outbreaks, surveillance need be established in hospitals in China.

Conflict of interest statement

None declared.

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