

Epidemiological characteristics and clinical manifestations of pediatric patients with COVID-19 in China: A multicenter retrospective study

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ABSTRACT

Importance: The Coronavirus disease 2019 (COVID-19) global pandemic poses a considerable challenge for pediatricians.

Objective: This study aimed to identify the epidemiological characteristics and clinical features of pediatric patients with COVID-19 in China.

Methods: This multicenter retrospective study included pediatric patients from 46 hospitals in China, covering 12 provinces and two municipalities. Epidemiological, demographic, clinical, laboratory, treatment, and outcome data were analyzed.

Results: In total, 211 pediatric patients with COVID-19 were included in this study. The median age was 7.0 years (range: 22 days to 18 years). Approximately 16.3% of the patients exhibited asymptomatic infections, 23.0% had upper respiratory tract infections, and 60.7% had pneumonia, including two with severe pneumonia and one with critical illness. Approximately 78.7% of the pediatric patients occurred in familial clusters. The most three common symptoms or signs at onset in children with COVID-19 were fever (54.5%), cough (49.3%), and pharyngeal congestion (20.8%). Only 17.6% of the patients presented with decreased lymphocyte count, whereas 13.6% had increased lymphocyte count. Among the patients with pneumonia who exhibited abnormal chest computed tomography findings, 18.2% (23/127) of the patients had no other symptoms. Generally, the chest radiographs showed abnormalities that affected both lungs (49.6%); ground-glass opacity (47.2%) was the most common manifestation. The cure and improvement rates were 86.7% (183/211) and 13.3% (28/211), respectively. Only one patient with an underlying condition received invasive mechanical ventilation; none of the patients died.

Interpretation: Similar to adults, children of all age groups are susceptible to COVID-19. Fortunately, most pediatric patients have mild symptoms or remain asymptomatic, despite the high incidence of pneumonia. Decreased proportions of white blood cells and lymphocytes are less frequent in children than in adults.

KEYWORDS

COVID-19, SARS-CoV-2, Children

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INTRODUCTION

In December 2019, an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, was first reported in Wuhan, Hubei Province, China.¹⁻³ As of January 11, 2021, coronavirus disease 2019 (COVID-19) had affected 90 669 019 individuals and resulted in 1 942 512 deaths.⁴ People of all ages are susceptible to COVID-19. As a vulnerable group, children have received particular attention. Fortunately, compared with adult patients, the number of pediatric patients remains lower and their prognosis is better. A systematic review showed that the incidence of the disease in children comprised only 1%–6.4% of the total cases in multiple countries; moreover, the mortality rate was lower in children than in adults.⁵ One study revealed that only 5.6% (112/2143) of infected children developed severe disease (i.e., hypoxia), whereas only 0.6% developed multi-organ failure or acute respiratory distress syndrome.⁶ The mortality rate is less than 1% in children. Nevertheless, because of the global COVID-19 pandemic, there has been a growing number of reported pediatric patients, which poses a considerable challenge for pediatricians. Thus, to gain more knowledge regarding COVID-19 in pediatric patients, we analyzed the epidemiological and clinical features of 211 COVID-19 pediatric patients from 46 hospitals in China.

METHODS

Ethical approval

The study design was in accordance with the Helsinki Declaration and was approved by the Beijing Children's Hospital Ethics Committee (Approval number 2020-K-20). Because this was a retrospective study and data were analyzed anonymously, informed consent was waived.

Study design and participants

This multicenter study included pediatric inpatients (≤ 18 years old) with confirmed COVID-19 diagnosis, from 46 hospitals in China—12 provinces [Hubei except Wuhan (51), Guangdong (46), Hunan (37), Anhui (25), Guizhou (18), Shandong (9), Henan (5), Guangxi (4), Hainan (3), Hebei (3), Heilongjiang (2), Jilin (1)] and two province-level municipalities [Beijing (4) and Tianjin (3)]—between January 16, 2020 and February 25, 2020. Epidemiological, demographic, clinical, laboratory, treatment, and outcome data were extracted from electronic medical records using a standardized data collection form.

Diagnostic criteria for COVID-19^{7,8}

Patients who had epidemiological history and any two clinical manifestations matching the diagnostic criteria were suspected to have SARS-CoV-2 infection: 1) the patients had symptoms of fever, fatigue, and/or dry cough; 2) chest imaging showed bilateral multiple ground-glass opacity and/or obvious infiltrating shadows in the

lung periphery); 3) during the early phase of the disease, white blood cell counts were normal or decreased, or the lymphocyte count was decreased. Confirmed cases of COVID-19 were defined as “suspected patients who had tested positive for SARS-CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR) assay on nasal and pharyngeal swab specimens”. Clinical classifications were defined in accordance with previous reports.^{7,8}

1. Asymptomatic infection (silent infection) was recorded for children who tested positive for SARS-CoV-2 infection, but did not exhibit corresponding clinical symptoms or abnormal chest imaging findings.
2. Acute upper respiratory tract infection was recorded for children who exhibited symptoms such as fever, cough, pharyngeal pain, nasal congestion, fatigue, headache, myalgia, or discomfort; however, they did not demonstrate sepsis or signs of pneumonia according to chest imaging analysis.
3. Pneumonia was recorded for children who had respiratory symptoms such as fever, cough, tachypnea, and chest imaging alterations. These patients were subdivided into mild, severe, and critically ill patients, as follows.

Mild pneumonia referred to patients that did or did not involve fever, respiratory symptoms (e.g., cough), and chest imaging findings indicative of pneumonia; however, the manifestations did not meet the criteria for severe pneumonia.

Severe pneumonia referred to patients that met any of the following criteria: 1) increased respiratory rate: ≥ 70 breaths/min (for children under 1 year of age) or ≥ 50 breaths/min (for children above 1 year of age), following the exclusion of potential interference caused by fever or crying; 2) oxygen saturation $< 92\%$; 3) hypoxia: assisted breathing (e.g., moans, nasal flaring, and/or retractions of supraclavicular, substernal, and intercostal spaces), cyanosis, and/or intermittent apnea; 4) disturbance of consciousness: somnolence, coma, or convulsion; 5) food refusal or feeding difficulty, with signs of dehydration.

Critically ill patients referred to patients who met any of the following criteria and required admission to the intensive care unit: 1) respiratory failure requiring mechanical ventilation; 2) shock; and 3) multi-organ failure.

Other definitions

The incubation period was defined as the interval between the putative earliest date of contact with the infectious source (i.e., person with suspected or confirmed infection) and the earliest date of symptom onset (e.g., cough, fever, fatigue, or myalgia). Lymphocytopenia was defined in accordance with the standards in the *Zhu Futang Textbook of Pediatrics* [reference ranges: $(2.9-8.8) \times 10^9/L$ (< 3

months), $(3.6-8.8) \times 10^9/L$ (4-8 months), $(2.1-8.2) \times 10^9/L$ (9 months to 2 years), and $(2.0-2.7) \times 10^9/L$ (3-18 years)].⁹

Statistical analysis

All analyses were conducted with SPSS Statistics, version 22.0. The Wilcoxon rank-sum test was used to compare continuous variables, while Fisher’s exact test was used to compare categorical variables. Results were considered statistically significant when $P < 0.05$.

RESULTS

Demographic and epidemiological features of pediatric patients

In total, 211 pediatric patients with COVID-19 were included in this study (107 girls and 104 boys); the median age was 7.0 years (range: 22 days to 18 years). Most patients (34.1%, 72/211) were aged 6-12 years. The age distribution of the patients is shown in Table 1. Among the 211 patients, two did not undergo chest imaging examinations and thus could not be classified in any clinical group. In this study, COVID-19 clinical statuses included asymptomatic infection (16.3%, 34/209), upper respiratory tract infection (23.0%, 48/209), and pneumonia (60.7%, 127/209). The forms of pneumonia were mild ($n = 124$, 59.3%), severe ($n = 2$), and critical ($n = 1$). Among the 211 patients, 12 (5.7%) had underlying conditions,

including preterm birth ($n = 4$), recurrent respiratory tract infection ($n = 6$), congenital heart disease ($n = 3$), asthma ($n = 2$), suspected primary immunodeficiency ($n = 2$), epilepsy ($n = 1$), and tumor ($n = 1$). Eleven of the patients with underlying conditions were diagnosed with mild pneumonia, while one was critically ill.

Approximately 82.5% (174/211) of the patients had a history of exposure or contact with confirmed COVID-19 patients, 33.2% (70/211) had a history of travel to or residence in Wuhan, and two had a history of exposure to the South China Seafood Market. Moreover, 78.7% (166/211) of the patients occurred in familial clusters of infection (Table 1). The median incubation time was 10 days (range: 1-34 days). The median interval from symptom onset to disease confirmation was 1 day (range: 0-14 days).

Clinical features

The most common sign or symptom at the onset of disease was fever (54.5%, 115/211), defined as a body temperature $> 37.3^\circ C$. Approximately 43.1% of the patients had low-grade fever ($37.3-38.0^\circ C$); a few patients (17.2%) exhibited high-degree fever ($> 39.0^\circ C$). The median duration of fever was 2.5 days (range: 0.5-20 days), while two patients exhibited persistent fever for 20 days. The second most common symptom was cough (49.3%, 104/211); 57 patients exhibited dry cough and 47 patients

TABLE 1 Epidemiological and clinical features of pediatric patients with COVID-19 in China

Clinical features	Total ($n = 211$) [*]	Asymptomatic infection ($n = 34$) [*]	Upper respiratory tract infection ($n = 48$) [*]	Pneumonia ($n = 127$) [*]
Age group (year)				
< 1	19 (9.0)	0	1 (2.1)	18 (14.2)
1- < 3	38 (18.0)	3 (8.8)	9 (18.8)	25 (19.7)
3- < 6	33 (15.6)	6 (17.6)	7 (14.6)	19 (15.0)
6- < 12	72 (34.1)	12 (35.3)	23 (47.9)	37 (29.1)
≥ 12	49 (23.2)	13 (38.2)	8 (16.6)	28 (22.0)
Female	107 (50.7)	16 (47.1)	24 (50.0)	66 (52.0)
Epidemiological history				
History of exposure or contact with COVID-19 confirmed cases	174 (82.5)	31 (91.2)	40 (83.3)	102 (80.3)
Travel or residence history in Wuhan City	70 (33.2)	8 (23.5)	19 (39.6)	43 (33.9)
Family cluster outbreak	166 (78.7)	27 (79.4)	41 (85.4)	97 (76.4)
Main symptoms and signs				
Fever	115 (54.5)	0	32 (66.7)	81 (63.8)
Cough	104 (49.3)	0	25 (52.1)	78 (61.4)
Pharyngeal congestion	44 (20.9)	0	10 (20.8)	34 (26.8)
Gastrointestinal symptoms	22 (10.4)	0	3 (6.3)	19 (15.0)
Diarrhea	11 (5.2)	0	1 (2.1)	10 (7.9)
Anorexia	10 (4.7)	0	1 (2.1)	9 (7.1)
Vomiting	5 (2.4)	0	0	5 (3.9)
Abdominal pain	1 (0.5)	0	1 (2.1)	0
Fatigue	5 (2.4)	0	1 (2.1)	4 (3.1)
Headache	4 (1.9)	0	2 (4.2)	2 (1.6)
Dyspnea	2 (0.9)	0	0	2 (1.6)
Abnormal lung auscultation	21 (10.0)	0	1 (2.1)	20 (15.7)

Data are presented as n (%). ^{*}Among the 211 patients, two did not undergo chest imaging examinations and thus could not be classified in any of the three groups (asymptomatic infection group, upper respiratory tract infection group and pneumonia group). COVID-19, coronavirus disease 2019.

exhibited productive cough. The median duration of cough was 8.5 days (range: 1–32 days). Additionally, pharyngeal congestion, gastrointestinal symptoms (e.g., nausea and/or vomiting, and diarrhea), fatigue, and headache were recorded in 20.8%, 10.7%, 2.4%, and 1.9% of the patients, respectively (Table 1). Only one patient developed respiratory failure and required invasive mechanical ventilation. Lung auscultation abnormalities were observed in 10.0% (21/211) of the patients: 10 with fine rales, 10 with coarse rales, and one with wheeze. In total, 127 patients showed radiologic features of pneumonia, among which 23 (18.2%) had no other symptom of infection. No pediatric patients developed multisystem inflammatory syndrome in this study.

Laboratory characteristics

In total, 199 pediatric patients were tested for full blood cell count. Most patients had normal white blood cell (WBC) counts (85.9%, 171/199), 26 had leukocytosis, and two had decreased WBC counts. The median lymphocyte count was $2.4 \times 10^9/L$ [range: $(0.7\text{--}9.5) \times 10^9/L$]; 17.6% of the patients had decreased lymphocyte count. The C-reactive protein concentration was increased in 20.1% (32/159) of the patients; the median concentration was 16.3 mg/L (range: 8.7–47.1 mg/L; reference range: < 8 mg/L). The procalcitonin concentration was increased in 14.5% (17/117) of the patients. Liver function assessment revealed that 6.2% of the patients had an increased alanine aminotransferase concentration (reference range: < 40 U/L); heart function assessment indicated that 12.9% of the patients had increased creatinine kinase-MB concentration (reference range: < 25 U/L) and two patients had an increased troponin concentration. Except for the one

patient with critical illness, all patients had normal renal function (Table 2). Levels of IgG, IgA, and IgM were normal in most patients, as were the numbers of CD4⁺ T cells, CD8⁺ T cells, B cells, and NK cells.

All patients were confirmed to have SARS-CoV-2 infection according to viral nucleic acid analysis. The median interval from positive SARS-CoV-2 results to negative SARS-CoV-2 results according to throat swab analysis was 8 days. Additionally, 11 patients exhibited positive SARS-CoV-2 results according to rectal swab analysis at days 2, 3, 8, 11, 16, and 19 (three patients), and until days 21 and 22 (two patients) after diagnosis. Only one case exhibited recurrent positive SARS-CoV-2 results (for an interval of 4 days) according to throat swab analysis, following discharge 5 days prior; notably, that patient had no additional symptoms. Patients with other identified pathogens included four patients of influenza virus type A, two patients of influenza virus type B, and two patients of *Mycoplasma pneumoniae*. All eight co-infected patients had pneumonia.

Radiological characteristics

Chest radiographs were performed for 209 patients; abnormalities were visible in 60.8% (127/209) of patients. Among these patients, there were 63 patients (49.6%) with bilateral lung involvement, 38 patients (30.0%) with unilateral right lung involvement, and 26 patients (20.4%) with unilateral left lung involvement (Table 3). The most common feature on chest radiography was ground-glass opacity (47.2%), followed by patchy shadows (40.2%), and a combination of ground-glass opacity with patchy shadows (12.6%). There were no patients with pleural

TABLE 2 Laboratory features of pediatric patients with COVID-19 in China

Clinical features	Total (n = 199) [†]	Asymptomatic infection (n = 32) [‡]	Upper respiratory tract infection (n = 44) [‡]	Pneumonia (n = 121) [‡]
White blood cells count				
Normal	171/199 (85.9)	31/32 (96.9)	35/44 (79.5)	103/121 (85.1)
Decreased	2/199 (0.1)	0/32 (0.0)	0/44 (0.0)	2/121 (1.7)
Increased	26/199 (13.1)	1/32 (3.1)	9/44 (20.5)	16/121 (13.2)
Lymphocytes				
Normal	137/199 (68.8)	23/32 (71.8)	27/44 (61.4)	85/121 (70.2)
Decreased	35/199 (17.6)	6/32 (18.8)	7/44 (15.9)	22/121 (18.2)
Increased	27/199 (13.6)	3/32 (9.4)	10/44 (22.7)	14/121 (11.6)
Increased CRP	32/159 (20.1)	1/20 (5.0)	5/39 (12.8)	26/99 (26.3)
Increased PCT	17/117 (14.5)	3/19 (15.8)	6/27 (22.2)	8/70 (11.4)
Abnormal ALT	11/177 (6.2)	0/29 (0.0)	3/40 (7.5)	8/107 (7.5)
Abnormal CK-MB	22/171 (12.9)	1/28 (3.6)	6/41 (12.2)	15/101 (14.9)
Abnormal D-dimer	46/138 (33.3)	8/22 (36.4)	11/30 (36.7)	27/86 (31.4)
Abnormal LDH	42/163 (25.8)	2/27 (7.4)	6/36 (16.7)	34/99 (34.3)

Data are presented as n/N (%). [†]Not all of the 199 patients performed the following laboratory tests. [‡]The 199 patients included two cases who cannot be divided into any of the three groups (asymptomatic infection group, upper respiratory tract infection group or pneumonia group) because they did not undergo chest imaging exam. Reference ranges: white blood cells, $(4\text{--}10) \times 10^9/L$; lymphocytes, $(2.9\text{--}8.8) \times 10^9/L$ (< 3 months), $(3.6\text{--}8.8) \times 10^9/L$ (4 months to 8 months), $(2.1\text{--}8.2) \times 10^9/L$ (9 months to 2 years), $(2.0\text{--}2.7) \times 10^9/L$ (3–18 years); C-reactive protein (CRP) < 8 mg/L; procalcitonin (PCT) < 0.25 ng/mL; alanine aminotransferase (ALT), ≤ 40 U/L; creatine kinase MB (CKMB), < 25 U/L; D-dimer, < 0.25 mg/L; serum lactic dehydrogenase (LDH), < 295 U/L. COVID-19, coronavirus disease 2019.

TABLE 3 The image findings of pediatric patients with SARS-CoV-2 pneumonia in China

Radiographic pattern	Total (n = 127)	< 1y (n = 18)	1- < 3y (n = 25)	3- < 6y (n = 19)	6- < 12y (n = 37)	≥12y (n = 28)
Location						
Both lungs	63 (49.6)	11 (61.1)	19 (76.0)	9 (47.4)	12 (32.4)	12 (42.9)
Unilateral right lung	38 (30.0)	4 (22.2)	6 (24.0)	4 (21.1)	13 (35.1)	11 (39.3)
Unilateral left lung	26 (20.4)	3 (16.7)	0 (0)	6 (31.5)	12 (32.4)	5 (17.8)
Abnormal findings						
Ground-glass opacity	60 (47.2)	9 (50.0)	11 (44.0)	7 (36.8)	14 (37.8)	19 (67.9)
Patchy	51 (40.2)	7 (38.9)	13 (52.0)	8 (42.1)	17 (45.9)	6 (21.4)
Both	16 (12.6)	2 (11.1)	1 (4.0)	4 (21.1)	6 (16.3)	3 (10.7)

Data are presented as n (%). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

effusion in this study. Radiographic images from two patients with severe pneumonia and one case with critical illness showed bilateral lung involvement.

Treatments and clinical outcomes

In total, 196 patients received anti-viral treatment, including 124 patients treated with interferon alpha; the remaining patients were treated with either oseltamivir, Arbidol, ribavirin, or lopinavir/ritonavir. Intravenous immunoglobulins and systemic corticosteroids were used in the treatment of two patients with severe pneumonia and one case with critical illness for 3–4 days. Moreover, the patient with critical illness received mechanical ventilation. This patient had suspected immunodeficiency and a history of open-heart surgery due to congenital heart disease. Additionally, some patients were treated with traditional Chinese medicine. All 211 patients had improved conditions and were cured eventually. None of the included patients died.

DISCUSSION

At the beginning of the COVID-19 outbreak, most confirmed patients were adults. Over time, an increasing number of pediatric patients were reported.^{6,10-12} Ludvigsson’s¹³ systematic review of 45 relevant scientific papers and letters showed that, compared with adults, pediatric patients comprised fewer than 7% of the diagnosed patients of COVID-19; moreover, pediatric patients often exhibited milder disease and rarely died. These results are similar to the findings of our study, in that all pediatric patients had good prognosis. Compared with adults, children with COVID-19 demonstrate a milder clinical course. Previous studies reported that children with COVID-19 were hospitalized less frequently than adults with COVID-19; furthermore, fewer children with COVID-19 experienced fever, cough, or shortness of breath.^{11,14} Khamis et al¹⁵ compiled the clinical characteristics of adult patients and showed that the fatality rate was 10.5%.

The good clinical outcomes of COVID-19 in pediatric

patients, compared with adult patients, are reminiscent of the differences between children and adults during infections with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS). Children reportedly had much milder courses of SARS-CoV and MERS-CoV infections, compared with adults. No pediatric deaths were reportedly caused by SARS, while only two pediatric deaths were reportedly caused by MERS.¹⁶⁻¹⁸ The reasons for lower numbers of infections and severity in children are unclear and might be related to the intrinsic features of children. First, children may be less physiologically susceptible to SARS-CoV-2 because they exhibit lower expression levels of angiotensin-converting enzyme 2 (ACE2) receptors in lung tissue.¹⁹ Second, the immaturity of the pediatric immune system might prevent severe immunopathological injuries, which are important in the immunopathology of COVID-19 infection in adults.²⁰

Children of all ages are susceptible to COVID-19, and most studied patients were previously healthy. Our study found that the median age (7.0 years) of children with COVID-19 was similar to the age range reported in previous studies (7–11 years).^{10,21} A study performed in the United States revealed that 10.6% of infants developed severe COVID-19, compared with 5.8% of older children.¹¹ This finding indicated that infants infected with SARS-CoV-2 develop more severe disease, need more attention, and should be further protected. In our study, 83.3% of the pediatric patients had a history of exposure or contact with confirmed COVID-19 patients, and 78.7% had been infected during outbreaks in family clusters. These findings were similar to the results in previous studies.^{10,11} In the United States, the incidence related to outbreaks in family clusters was 91%.⁶ Thus, for the diagnosis of COVID-19 in pediatric patients, the epidemiological history is a prominent factor.

The three most common symptoms or signs at onset of COVID-19 found in this study were fever (54.5%), cough (49.3%), and pharyngeal congestion (20.8%), consistent with the findings in previous studies.^{10,11} In

contrast, the most common symptoms in adults were fever (98%), cough (76%), and fatigue (44%).¹⁹ Contrary to adults, 45.5% of pediatric patients were afebrile; most febrile children had low to moderate fever. In addition, the proportion of dyspnea was much lower in pediatric patients than in adult patients. Only one child with respiratory failure required mechanical ventilation support in this study. Furthermore, only 14.1% of the patients had decreased WBC count, while 17.6% had decreased lymphocyte count, which is similar to the results in a previous study.¹³ Presumably, SARS-CoV-2 directly destroys T lymphocytes by binding their ACE2 receptors, thus decreasing their counts. Because the expression of ACE2 receptors on T lymphocytes is considerably lower in children than in adults, the decreases in WBC and lymphocyte counts mainly occur in adults.²²

The clinical symptoms and signs of COVID-19 in pediatric patients are similar to the symptoms and signs of other respiratory virus infections in pediatric patients. Fever and cough are the most common symptoms, both in SARS-CoV-2 pneumonia and pneumonias caused by other respiratory pathogens. Compared with influenza A pneumonia in children under 5 years of age, comparatively lower proportions of fever, cough, sputum production, shortness of breath, and abnormal pulmonary auscultation were observed in pediatric patients with COVID-19.²³ Lymphopenia was also found in patients with severe influenza and other respiratory viral infections. Nevertheless, the clinical, epidemiological, and radiological features of COVID-19 might help to distinguish it from other respiratory viral infections.²⁴

In addition, since April 2020, clinicians in the United Kingdom, Italy, and the United States have reported a rare and severe inflammatory syndrome in children with COVID-19 [i.e., multisystem inflammatory syndrome in children (MIS-C)]. Affected children exhibit multiple system dysfunction, including manifestations similar to typical Kawasaki disease; these range from inflammation to myocardial injury, shock, coronary artery aneurysms, and mucocutaneous manifestations. However, these manifestations are rarely concomitant with respiratory symptoms²⁵ and imply a diffuse inflammatory process.²⁶ Our study did not identify any case with MIS-C, and further clinical observations are needed to detect such patients.

This study had a few limitations. First, it was a retrospective multi-center study; included patients were treated at one of 46 hospitals. Therefore, some information was incomplete. Second, we could not evaluate the efficacies of the drugs that were used to treat children with COVID-19. A randomized controlled trial is needed to determine the optimal treatment.

In conclusion, children of all ages are susceptible to COVID-19, but the greatest proportion of patients

occurred in children aged 6–12 years. Most pediatric patients with COVID-19 had a milder disease course and better prognosis, compared with adults. The proportions of leukopenia and lymphopenia were lower in affected children than in affected adults. Children who were exposed to family clusters of infection or had contact with a confirmed case should be tested to ensure a timely diagnosis.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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