

# Severe Acute Respiratory Syndrome–Associated Coronavirus Infection in Toronto Children: A Second Look

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The authors have indicated they have no financial relationships relevant to this article to disclose.

## What's Known on This Subject

The clinical course of SARS-CoV infection tends to be milder in young children compared with teenagers and adults. Young children also seem to be less infectious than older persons. Most of the pediatric experience with SARS-CoV infection is from Southeast Asia.

## What This Study Adds

This study cohort represents the only North American experience with SARS-CoV infection in children. The importance of epidemiology in case detection is a key finding. Additional evidence for the mild nature of SARS-CoV infection in children <12 years of age is provided.

## ABSTRACT

**OBJECTIVES.** During the severe acute respiratory syndrome outbreak of 2003, there was an impetus to provide clinical information to the medical community in a timely manner. Accordingly, a preliminary report of our experience of suspected severe acute respiratory syndrome–associated coronavirus infections in children was published without microbiological findings. This report provides an update on pediatric severe acute respiratory syndrome–associated coronavirus infections in Toronto, Ontario, Canada, that includes microbiological findings.

**METHODS.** All of the children admitted to the Hospital for Sick Children between March 14 and June 15, 2003, with suspect severe acute respiratory syndrome–associated coronavirus infection were included. A proven case was defined as one that fulfilled the clinical criteria for suspect severe acute respiratory syndrome–associated coronavirus infection and demonstrated a serologic response to severe acute respiratory syndrome–associated coronavirus. Serology results, from a neutralizing antibody assay, were considered positive if the sera inhibited the development of a severe acute respiratory syndrome–associated coronavirus-specific cytopathic effect at a dilution of  $\geq 1:8$ .

**RESULTS.** Neutralizing antibody to severe acute respiratory syndrome–associated coronavirus was demonstrated in 8 of 25 children admitted with suspect severe acute respiratory syndrome–associated coronavirus infection. In 3 of these 8 children, severe acute respiratory syndrome–associated coronavirus was also detected by reverse-transcription polymerase chain reaction in the stool. All 8 had documented exposure to  $\geq 1$  severe acute respiratory syndrome–associated coronavirus-infected adults residing in the same household. Exposure that was limited to visiting a Toronto hospital at which severe acute respiratory syndrome–associated coronavirus-infected patients were admitted or travel from a country in which severe acute respiratory syndrome had been reported did not result in documented infection in any of our cases. On the basis of our clinical case definition, 6 of 8 microbiologically confirmed case had been classified as having probable severe acute respiratory syndrome–associated coronavirus infection. Clinical disease was mild, nonspecific, and self-limited and was indistinguishable from that reported with other common respiratory viruses.

**CONCLUSIONS.** The factor most strongly associated with severe acute respiratory syndrome–associated coronavirus infection in Toronto children was a history of close contact with an adult severe acute respiratory syndrome–associated coronavirus case. This serves to reinforce the importance of routinely obtaining a thorough epidemiologic travel and exposure history for all subjects with suspected infectious diseases. *Pediatrics* 2009;123:97–101

[www.pediatrics.org/cgi/doi/10.1542/peds.2007-3745](http://www.pediatrics.org/cgi/doi/10.1542/peds.2007-3745)

doi:10.1542/peds.2007-3745

### Key Words

severe acute respiratory syndrome, SARS, reverse-transcription polymerase chain reaction, probable SARS, suspect SARS

### Abbreviations

SARS—severe acute respiratory syndrome  
CoV—associated coronavirus  
RT-PCR—reverse-transcription polymerase chain reaction

Accepted for publication Mar 25, 2008

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**H**ORSESHOE BATS in southern China have been shown recently to be the natural reservoir for coronaviruses phylogenetically closely related to the severe acute respiratory syndrome–associated coronavirus (SARS-CoV).<sup>1,2</sup> It has also been shown that SARS-CoV is capable of infecting a wide range of wild and domestic mammals.<sup>3,4</sup> Given the frequent close contact of humans with animals potentially infected with SARS-CoV or related viruses in

the wet markets of southern China and to a lesser extent in the wild, it is quite possible that SARS-CoV or a related virus could be reintroduced into the human population in the future.

We described previously the clinical, laboratory, and radiographic features of children with suspect or probable SARS-CoV infection admitted to the Hospital for Sick Children during the SARS outbreak that occurred in Toronto, Ontario, Canada, between March and June of 2003.<sup>5</sup> In that report, children were categorized on the basis of potential SARS exposure, clinical features, and the presence or absence of an alternative microbiological diagnosis. In this report we provide an update on pediatric SARS-CoV infection in Toronto based on microbiological diagnosis.

## METHODS

All of the children admitted to the Hospital for Sick Children between March 14 and June 15, 2003, with suspect SARS were included in this report. The clinical case definitions and management protocol used during the SARS outbreak were described in our previous report.<sup>5</sup> Briefly, children were classified as having suspect SARS-CoV infection if they had a history of possible SARS exposure and fever ( $>38^{\circ}\text{C}$ ). A probable case was defined as suspect SARS-CoV infection plus severe progressive respiratory illness and/or chest radiograph findings indicative of lower respiratory tract disease without microbiological evidence implicating another causative agent. Possible SARS-CoV infection was defined as a suspect case without the aforementioned clinical and radiographic criteria for probable SARS-CoV infection without microbiological evidence implicating another causative agent. The "other etiology" category was reserved for those in whom another causative agent was identified. In the current report, a proven case of SARS-CoV infection was defined as one that fulfilled the clinical criteria for suspect SARS-CoV infection and demonstrated neutralizing antibody to SARS-CoV in acute and convalescent sera. Those fulfilling the clinical case definition for suspect SARS-CoV infection who were seronegative in their acute and convalescent sera were accordingly defined as non-SARS-CoV case subjects.

SARS-CoV serology was performed by a neutralizing antibody assay in a dedicated biosafety level III facility at the British Columbia Center for Disease Control.<sup>6</sup> Sera were tested for their ability to neutralize the virus from dilutions of 1:8 to 1:4096. Acute and/or convalescent sera that exhibited viral neutralization at a dilution of  $\geq 1:8$  were deemed positive for neutralizing antibody.

Reverse-transcription polymerase chain reaction (RT-PCR) on stool and nasopharyngeal specimens was performed as follows. A 10% suspension of the stool in double-distilled water was clarified by centrifugation and the supernatant fraction processed for nucleic acid extraction. The specimens containing the nasopharyngeal swabs were agitated on a vortex mixer and the transport medium subjected to nucleic acid extraction. RNA was extracted from the specimens by a semiautomated method, using the MagaZorb RNA kit (Cortex Biochem, Inc, San Leandro, CA) with the KingFisher

instrument (Thermo Electron Corp, Waltham, MA). Each sample was tested with 2 different assays, an "in-house" assay for coronaviruses,<sup>7</sup> and a commercial assay, the Real Art HPA Coronavirus RT-PCR (Artus GmbH, Hamburg, Germany).

## RESULTS

Twenty-five children were admitted to the Hospital for Sick Children between March 14 and June 15, 2003, with a diagnosis of suspect SARS-CoV infection. Neutralizing antibody to the SARS-CoV was demonstrated in 8 of these children. SARS-CoV RNA was detected by RT-PCR in the stool of 3 children by both RT-PCR methods; all 3 also had a neutralizing antibody to the virus. The timing of viral detection in stool ranged from day 5 to day 7 of illness. Thirteen nasopharyngeal swabs and 8 nasopharyngeal aspirates on 15 patients were tested and found to be negative by the real-time RT-PCR assay. In 1 patient with serologically confirmed SARS-CoV infection, coinfection with adenovirus was demonstrated by the detection of adenovirus antigen in a nasopharyngeal swab. In 9 of the 17 children with negative SARS-CoV serology results, an alternate etiology was identified, including influenza A virus ( $n = 3$ ), parainfluenza 3 virus ( $n = 1$ ), respiratory syncytial virus ( $n = 1$ ), adenovirus ( $n = 1$ ), varicella zoster virus ( $n = 1$ ), rotavirus ( $n = 1$ ), and *Streptococcus pneumoniae* ( $n = 1$ ). According to the clinical diagnostic criteria used during the SARS outbreak, 6 serologically confirmed cases had been classified as probable SARS-CoV infections, 1 as a possible SARS-CoV infection, and 1 as having another etiology.

The clinical, laboratory, and radiographic features of serologically confirmed SARS-CoV cases are shown in Table 1, and a comparison of clinical and laboratory features of SARS-CoV and non-SARS-CoV cases is given in Table 2. Although the clinical manifestations of those with and without SARS-CoV infection were indistinguishable, respiratory symptoms were observed in only 3 children (37.5%) in the former group. However, chest radiograph abnormalities consisting predominantly of focal infiltrates were noted in 87.5% (7 of 8) of SARS-CoV cases compared with 29% (5 of 17) of non-SARS-CoV cases (Fisher's exact test,  $P = .01$ ). Diarrhea occurred in 2 children with SARS-CoV infection. Importantly, with the exception of one 17.5-year-old girl who required supplemental oxygen by nasal prongs, the illness was so mild that hospital admission and/or supportive therapy of any kind would not have been needed had SARS not been a consideration.<sup>5</sup>

Hematologic abnormalities were noted in the majority of SARS-CoV infections. At the time of admission, leukopenia was observed in 50% (4 of 8) of those with compared with 6% (1 of 17) of those without SARS-CoV infection (Fisher's exact test,  $P = .02$ ). Lymphopenia was also more common in the SARS-CoV group at admission (50% vs 18%; Fisher's exact test,  $P = .16$ ), whereas neutropenia was relatively uncommon, occurring in only 1 child in each group. During the course of hospitalization, leukopenia was seen in 75.0% (6 of 8) and neutropenia in 62.5% (5 of 8) of SARS-CoV infections compared with 18.0% (3 of 17) for both parameters in

**TABLE 1 Clinical and Laboratory Features of SARS-CoV-Infected Patients**

Case	Age, y	Gender	$T_{\max}$ , °C	Clinical Manifestations	Chest Radiograph Findings	Laboratory Abnormalities	SARS-CoV Neutralization Inhibition Titer, Acute/Convalescent <sup>a</sup>
1	17.5	F	40.1	Cough, dyspnea, hypoxemia, bilateral crackles	Dense RML and LLL infiltrate	Leukopenia ( $2.70 \times 10^9/L$ ); lymphopenia ( $0.81 \times 10^9/L$ ); thrombocytopenia ( $130 \times 10^9/L$ ); elevated AST, ALT (236 U/L, 187 U/L); elevated CPK (457 U/L); elevated LDH ( $>2150$ U/L)	<1:8/1:32
2	12	F	38.1	Cough, diarrhea	LLL infiltrate	None	<1:8/1:128
3	11	M	38.5	Headache, chills	RLL infiltrate	Lymphopenia ( $1.39 \times 10^9/L$ )	<1:8/1:256
4	6	M	38.2	Sore throat, vomiting	Patchy lower lobe infiltrate, peribronchial thickening	Lymphopenia ( $1.30 \times 10^9/L$ ); neutropenia ( $0.33 \times 10^9/L$ ); elevated AST (61 U/L); elevated LDH (1012 U/L)	1:64/1:128
5	5	F	40.3	Cough	Normal	Leukopenia ( $3.10 \times 10^9/L$ ); neutropenia ( $1.00 \times 10^9/L$ ); lymphopenia ( $1.30 \times 10^9/L$ )	ND/1:64
6	2.4	M	38.2	Lethargy	RLL infiltrate	Leukopenia ( $2.4 \times 10^9/L$ ); lymphopenia ( $0.74 \times 10^9/L$ ); neutropenia ( $0.63 \times 10^9/L$ )	<1:8/1:512
7	1.75	F	39.0	Diarrhea, lethargy	Multifocal perihilar and lower lobe patchy infiltrates	Neutropenia ( $1.4 \times 10^9/L$ )	1:8/1:64
8	0.4	M	39.0	Rhinorrhea	Patchy RUL and RLL infiltrates	Neutropenia ( $0.65 \times 10^9/L$ ); elevated AST, ALT (97 U/L, 74 U/L)	1:64/1:64

F indicates female; M, male; RUL, right upper lobe; RLL, right lower lobe; RML, right middle lobe; LLL, left lower lobe; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CPK, creatine kinase; LDH, lactate dehydrogenase;  $T_{\max}$ , maximum temperature.

<sup>a</sup> ND indicates not done; acute sample was not available for testing.

the non-SARS-CoV group (Fisher's exact test,  $P = .01$  and  $P = .06$ , respectively). In SARS-CoV-infected children, the nadir lymphocyte count occurred within 24 hours of hospitalization in 62.5% (5 of 8) of cases,

whereas the neutrophil nadir was seen between days 4 and 6 of hospitalization in a similar proportion. Alanine aminotransferase was slightly higher in the SARS-CoV group (Kruskal-Wallis test,  $P = .01$ ). There were no

**TABLE 2 Clinical and Laboratory Features of Children With and Without Serologically Confirmed SARS-CoV Infection**

Parameter	SARS-CoV ( $n = 8$ )	Non-SARS-CoV ( $n = 17$ )	$P^a$
Age, y	5.5 (2.1–11.5)	2.0 (1.2–3.0)	.14
Gender, % female	50	65	.67
Temperature, °C	38.4 (38.2–40.2)	39.3 (39.0–39.7)	.75
Cough, %	37.5	82.0	.06
Coryza, %	12.5	41.0	.20
Diarrhea, %	25.0	24.0	.99
CXR abnormalities, %	87.5	29.0	.01
Admission leukocyte count, $\times 10^9/L$	6.0 (4.1–11.6)	9.3 (6.3–11.1)	.17
Leukocyte count nadir, $\times 10^9/L$	4.0 (2.9–5.5)	8.2 (5.6–9.8)	.01
Admission neutrophil count, $\times 10^9/L$	2.5 (2.2–4.7)	5.24 (3.2–8.4)	.07
Neutrophil count nadir, $\times 10^9/L$	1.2 (0.6–1.8)	3.3 (1.9–5.5)	.01
Admission lymphocyte count, $\times 10^9/L$	1.6 (1.1–4.8)	2.5 (1.5–3.5)	.46
Lymphocyte count nadir, $\times 10^9/L$	1.3 (1.1–3.3)	2.1 (1.5–3.5)	.31
Admission platelet count, $\times 10^9/L$	312 (222–345)	254 (216–315)	.52
Platelet count nadir, $\times 10^9/L$	221 (158–264)	243 (172–294)	.41
ALT, U/L	34 (27–57)	16 (4–21)	.01
AST, U/L	42 (38–79)	41 (29–53)	.35
CPK, U/L	142 (101–200)	78 (57–160)	.07
LDH, U/L	1581 (1012–2150)	828 (733–850)	.12

Data are reported as medians (interquartile ranges) for continuous variables and proportions for dichotomous variables.

<sup>a</sup> Data were calculated by the Fisher's exact test for dichotomous variables and Kruskal-Wallis test for continuous variables.

**TABLE 3 SARS-CoV Infection According to Exposure Category**

Exposure Category	SARS-CoV Serology	
	Positive	Negative
Direct contact	8	3
Travel	0	9
Hospital	0	5

Direct contact with a SARS-CoV patient was predictive of SARS-CoV infection (Fisher's exact test,  $P < .0002$ ; direct contact versus other exposure).

differences between the 2 groups with respect to platelet count, aspartate aminotransferase, creatine kinase, or lactate dehydrogenase.

All 8 of the children with serologically confirmed SARS-CoV infection had documented exposure to  $\geq 1$  adult suspect or probable SARS case who resided in the same household (Table 3). By contrast, none of the 14 children with travel-related or hospital-related exposures were found to have SARS-CoV infection. Documented SARS exposure was, thus, highly predictive of SARS-CoV infection (Fisher's exact test,  $P < .0002$ ). The sensitivity, specificity, positive predictive value, and negative predictive value of documented direct exposure to a suspect SARS case were 100%, 82%, 73%, and 100%, respectively.

All 8 of the children confirmed to have been infected with SARS-CoV were seen in follow-up within 1 to 2 month of discharge. None reported any persistent or new symptoms, including fatigue, exercise intolerance, dyspnea, or wheezing. All of the caregivers and children felt that their health was fully restored. Four of the older children, including the 17-year-old who required oxygen while hospitalized, were seen 12 to 15 months after discharge and reported to be in good health. All had normal chest radiographs at this time. Pulmonary function testing, including prebronchodilator and postbronchodilator responses, was performed in the aforementioned 17-year-old and found to be normal.

## DISCUSSION

This series provides additional evidence that SARS-CoV infection in children is relatively mild and nonspecific and further supports our decision at the time of the outbreak to use less stringent clinical diagnostic criteria than those proposed by the World Health Organization. Although all children with microbiologically confirmed SARS-CoV infection had fever, only 3 (37.5%) of 8 had cough, and only 1 had dyspnea. Chest radiograph abnormalities consisting of minor nonspecific alveolar infiltrates were evident in 7 of 8 patients, in some despite the absence of respiratory symptoms. As has been observed by others,<sup>8,9</sup> the most reliable clue to the diagnosis was an epidemiological link to a suspected or confirmed SARS case. In our setting, all of the children with serologically confirmed SARS-CoV infection had documented exposure to at least 1 suspected adult case who resided in the same household. Although the degree to which this would hold true in the event of a future SARS-CoV outbreak is difficult to predict, it is likely that detection of potential cases on the basis of an epidemi-

ological link early in the course of an outbreak would allow for rapid and efficient containment of the outbreak. Based on our experience, as well as that of others,<sup>8,9</sup> we would recommend that, in the context of a SARS-CoV outbreak, any child with fever and an epidemiological link, particularly if  $<12$  years of age and irrespective of respiratory symptoms, be investigated for possible SARS-CoV infection.

Hematologic abnormalities are relatively common among children with SARS-CoV infection.<sup>8-14</sup> In our series, leukopenia at the time of admission and neutropenia during the course of hospitalization were more common in SARS-CoV-infected subjects than in uninfected subjects, although these observations are not likely to be sufficiently discriminatory for diagnostic purposes.<sup>9</sup> The nadir lymphocyte count tended to occur early in the course of illness, whereas neutropenia tended to develop later on, between days 4 and 6 of hospitalization. It is important to note that none of our children were treated with corticosteroids, a fact that could at least partially explain the absence of progressive lymphopenia that was observed in other studies.<sup>8,15</sup> It is also conceivable that, in mildly affected patients such as ours, progressive lymphopenia is less likely to develop.

The ability to rapidly and reliably confirm the diagnosis of SARS-CoV infection remains elusive because of the relative insensitivity of direct detection methodologies, such as RT-PCR, during the early phase of the illness, unless lower-respiratory tract samples are available for testing. SARS-CoV was detected in 47.7% of nasopharyngeal aspirates and in 38.6% of stool samples of serologically confirmed patients in the largest pediatric series published to date.<sup>8</sup> In most patients, SARS-CoV was detected in the nasopharynx during the first week of illness, whereas for stool samples this tended to occur 7 days into the illness or beyond. In our cohort, SARS-CoV was detected by RT-PCR in the stool of 37.5% of subjects between days 5 and 7 of illness, but in no child was it detected in nasopharyngeal samples. It is possible that our failure to detect the virus in the nasopharynx was a consequence of us obtaining samples within 24 hours of admission, a time when the viral burden in the nasopharynx may be quite low.<sup>16</sup>

The optimal timing for nasopharyngeal sampling for children with a mild and brief SARS-CoV illness has not been established, but it is likely that the viral burden in such children never reaches the levels observed in severely affected adolescents and adults in whom high viral loads peaking during the second week of illness are characteristic.<sup>16-18</sup> The diagnostic yield of 87.5% to 100.0% from plasma samples a mean of 7 days after the onset of fever in 1 small study, although promising, may not be applicable to less severely affected individuals and requires additional validation.<sup>17</sup> Given current knowledge, it would seem prudent to obtain repeated nasopharyngeal, throat, stool, and blood samples over time from children with suspected SARS-CoV infection or, for that matter, in the context of any outbreak associated with an unknown causative agent. Furthermore, as we observed with 1 child who was initially classified as having a non-SARS-CoV infection on the basis of an

alternate etiology (adenovirus), dual infections can occur.

Our experience suggests that the long-term prognosis of children infected with SARS-CoV infection is favorable. All 8 made full and complete recoveries with no clinical evidence of residual lung disease and normal follow-up chest radiographs. However, mild exercise intolerance and residual abnormalities on high-resolution computed tomographic scanning has been observed in some Hong Kong children 6 months after resolution of their acute illness.<sup>14,19</sup> These apparent differences are most likely related to differences in the severity of the acute illness; in our cohort, only 1 child required oxygen, and none needed ventilatory support compared with ~50% and 13%, respectively in the aforementioned Hong Kong cohort. Although unlikely given the mild nature of illness in our cohort, the possibility that we would have observed radiographic abnormalities with the use of high-resolution computed tomography cannot be excluded.

A limitation of this case series is its small size; with only 8 confirmed cases, it is difficult to draw firm conclusions regarding the typical clinical, laboratory, and radiographic features of SARS-CoV infection in children. Nevertheless, our findings are consistent with those of other pediatric case series and represent the entire cohort of infected children <14 years of age identified in Toronto during the outbreak; there were several older teenagers admitted to other institutions for whom we do not have clinical data. We were unable to comment on the sensitivity of RT-PCR in the respiratory tract at different time points of the illness, because nasopharyngeal sampling was restricted to the time of admission in most cases. Similarly, we did not evaluate the sensitivity of RT-PCR in blood or stool over time. Cross-reactivity of SARS-CoV serology with other coronaviruses is a potential concern, depending on the method used. However, the viral neutralization test used in our patients is the most specific serology test for SARS-CoV and is considered the reference test for this virus.<sup>20</sup>

## CONCLUSIONS

The nonspecific and relatively mild nature of SARS-CoV infection in young children and the importance of an epidemiological link in suspecting the diagnosis in children are consistent findings of the published literature.<sup>8,9,11</sup> Uncertainty with regard to the sensitivity of molecular testing for SARS-CoV in respiratory specimens in children remains a significant concern, particularly in those with relatively mild symptoms. The SARS-CoV outbreak of 2003 was, in a way, a fortuitous dress rehearsal that demonstrated the world's vulnerability to infectious diseases. Now, with an avian influenza pandemic looming, along with the possibility that a SARS-CoV-like virus could once again cross the species barrier into humans, the importance of routinely obtaining an epidemiological travel and exposure history for all subjects with suspected infectious diseases cannot be overemphasized.

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*Pediatrics* 2009;123;97

DOI: 10.1542/peds.2007-3745

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