

REGULAR ARTICLE

COVID-19 among children seeking primary paediatric care with signs of an acute infection

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Abstract

Aim: It can be challenging to distinguish COVID-19 in children from other common infections. We set out to determine the rate at which children consulting a primary care paediatrician with an acute infection are infected with SARS-CoV-2 and to compare distinct findings.

Method: In seven out-patient clinics, children aged 0–13 years with any new respiratory or gastrointestinal symptoms and presumed infection were invited to be tested for SARS-CoV-2. Factors that were correlated with testing positive were determined. Samples were collected from 25 January 2021 to 01 April 2021.

Results: Seven hundred and eighty-three children participated in the study (median age 3 years and 0 months, range 1 month to 12 years and 11 months). Three hundred and fifty-eight were female (45.7%). SARS-CoV-2 RNA was detected in 19 (2.4%). The most common symptoms in children with as well as without detectable SARS-CoV-2 RNA

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease of 2019; Ct, cycle threshold; OR, odds ratio; ORF, open reading frame; RNA, ribonucleic acid; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome virus 2.

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were rhinitis, fever and cough. Known recent exposure to a case of COVID-19 was significantly correlated with testing positive, but symptoms or clinical findings were not. **Conclusion:** COVID-19 among the children with symptoms of an acute infection was uncommon, and the clinical presentation did not differ significantly between children with and without evidence of an infection with SARS-CoV-2.

KEYWORDS

COVID-19, influenza, out-patient paediatrics, respiratory tract infection, SARS-CoV-2

1 | INTRODUCTION

A large range of clinical manifestations, from asymptomatic to severe disease, can be observed in patients of all age groups who are infected with severe acute respiratory symptom coronavirus 2 (SARS-CoV-2). Severe disease, however, is rare in children with coronavirus disease of 2019 (COVID-19), whereas asymptomatic infections are frequently observed.¹⁻⁵ When symptoms are present, cough, pharyngitis and fever are most prevalent. Nasal and gastrointestinal symptoms are reported to be less common,^{3,6} and symptom prevalence is dependent on the age of the child. There is a large overlap in the clinical presentation of COVID-19 when compared with other common respiratory pathogens.⁵

Identifying children with new symptoms of an acute infection who are infected with SARS-CoV-2 can be challenging. Factors that have previously been reported to be significantly associated with testing positive are recent contact with a person with known COVID-19, gatherings with persons outside of the household and lack of consistent mask use in schools.⁷ Among children who underwent testing for SARS-CoV-2, anosmia/ageusia, gastrointestinal symptoms and fever were strongly associated with testing positive.⁵ We are not aware of a study that compared the clinical findings of children, with and without evidence of SARS-CoV-2, in children seeking paediatric ambulatory medical care with symptoms of an acute infection.

The goal of this study was to determine the rate at which children up to and including the age of 12 years seeking ambulatory medical care at a primary care paediatrician's practice are experiencing the symptoms due to an infection with SARS-CoV-2. We also set out to determine whether items in the medical and exposure history or clinical findings can help clinicians determine which child warrants clinical suspicion of an infection with SARS-CoV-2. By also testing for influenza A and B, we set out to determine significant differences in the presentation of COVID-19 and influenza.

2 | METHODS

2.1 | Study sites and participants

This study was conducted in seven specialised primary care paediatric practices with a total of 13 practicing specialists in paediatrics from the larger Rhein-Main metropolitan region, Hesse, Germany.

Keynotes

- There are limited data to help clinicians discern the presentation of COVID-19 in children from other common causes of infection.
- At out-patient paediatric clinics, 783 children with symptoms of an acute infection were tested for SARS-CoV-2. Nineteen were positive (2.4%).
- Testing positive was significantly correlated with recent exposure to a known case of COVID-19; there were no significant differences in age distribution, symptoms or clinical findings.

Parents and their children, up to and including the age of 12 years, who presented to these clinics for consultation with symptoms of an acute infection, were invited to participate in the study. The presence of fever was not mandatory, and symptoms could include those of an airway infection, such as cough or rhinitis, or gastrointestinal symptoms, such as a stomach ache or diarrhoea. Testing for SARS-CoV-2 ribonucleic acid (RNA) was conducted independently of the local testing strategy and symptom severity. Only one test per episode of an illness was analysed. The caregivers were asked to fill in a questionnaire (Table S1) with questions about exposure history and symptoms. The paediatrician recorded the clinical findings in a standardised form (Table S2). The study duration was 25 January 2021 to 01 April 2021.

2.2 | Virological testing

Mid-turbinate nasal swabs were collected during the consultation of the study participants. Swabs were tested with the SARS-CoV-2 and Influenza A/B assay on the Cobas 6800 instrument (Roche diagnostics) according to manufacturer's instructions. This is a reverse transcription polymerase chain reaction (RT-PCR) assay using primers targeted at the E-gene and the open reading frame (ORF) 1 a/b non-structural region of SARS-CoV-2, respectively, and one target for the influenza A and influenza B virus, respectively. The number of cycles performed is 40.

In positive samples, key mutations of the SARS-CoV-2 variant of concern Alpha (B.1.1.7), N501Y, del69/70 and E484K were examined by melt curve analysis (VirSniP SARS-CoV-2 Spike N501Y, del69/70 and E484K assays; TIB Molbiol).

2.3 | Statistical analysis

Individual symptoms and medical history items were correlated with the positive detection of SARS-CoV-2 RNA in the nasal swab using a logistical regression model. Odds ratios (ORs), 95% confidence intervals (95% CI) and *p* values were calculated using Prism 9 (GraphPad Software Inc.).

2.4 | Patient consent and ethical approval

Written consent was obtained from the parents for all study participants. The study protocol has been approved by the ethics committee of the University Hospital Frankfurt, Goethe University Frankfurt, Germany.

3 | RESULTS

3.1 | Characterization and symptoms of study participants

A total of 783 children were enrolled in the study (Table 1). The median age was 3 years and 0 months (range 0 years and 1 month to 12 years and 11 months). Of these children, 358 were female (45.7%) and 425 were male. The most frequent symptoms reported by the caregivers were rhinitis (69.5%), cough (59.0%) and fever (31.8%). Gastrointestinal symptoms were less common, with 13.6% reporting stomach ache and 7.4% reporting diarrhoea (Table 2).

TABLE 1 Study participants by age group and positivity in the SARS-CoV-2 PCR test

Age group	Total number	SARS-CoV-2 negative	SARS-CoV-2 positive	95% CI
Newborn (0–1 month)	6	6	0	100.0% 0% [0.0%, 38.3%]
Infant (1 month–1 year)	105	102	3	97.1% 2.9% [0.5%, 8.1%]
Toddler (1–3 years)	286	279	7	97.6% 2.4% [1.0%, 5.0%]
Pre-school age (3–6 years)	232	229	3	98.7% 1.3% [0.3%, 3.7%]
School age (6–12 years)	154	148	6	96.1% 3.9% [1.4%, 8.2%]
All children	783	764	19	97.6% 2.4% [1.5%, 3.8%]

Abbreviation: CI, confidence interval.

3.2 | Results from virological testing

Reverse transcription polymerase chain reaction testing was valid in all 783 samples, as the internal control was correctly detected. Neither influenza A nor influenza B was detected in any of the swabs. Both RT-PCR targets of SARS-CoV-2 were detected in 18 samples (Table 1). Only one RT-PCR target of SARS-CoV-2 was detected in two samples: In one of these samples, only the ORF1 region was detected with a Ct value of 36.61. A follow-up sample tested positive for SARS-CoV-2 RNA in another laboratory, and the study participant was analysed as positive. In one sample, only the E-gene was detected with a Ct value of 36.86. A follow-up sample of this child was negative for SARS-CoV-2 RNA, and this study participant was analysed as negative.

The median cycle threshold (Ct) values of the positive samples were 22.37 for the ORF1-region target (range 16.28–36.61).

All newborns were tested negative for SARS-CoV-2 RNA. The positivity rate was low in all other age groups and ranged between 1.3% in children aged 3–6 years and 3.9% in children aged 6–12 years (Table 1).

3.3 | Characterization of cases of COVID-19

The median age of children with a positive detection of SARS-CoV-2 RNA was 3 years and 0 months (range 4 months to 11 years and 1 month) (Table 1).

Symptoms that were most frequently reported by the caregiver for the 19 cases of COVID-19 were rhinitis (57.9%), fever (47.4%) and cough (42.1%). The most common findings on clinical examination were obstructed nasal breathing (63.2%), rhinorrhoea (52.6%), pharyngitis (33.3%) and fever (31.6%) (Table 2).

There was no statistically significant correlation of any symptom or clinical finding with testing positive (Figure 1B,C). No child with COVID-19 had dyspnoea, tonsillitis (Table 3) or diarrhoea (Table 2).

Symptoms reported by caregiver	SARS-CoV-2 negative		SARS-CoV-2 positive		p value
	Symptom present (n)	(%)	Symptom present (n)	(%)	
Fever	240	31.9	9	47.4	0.17
Rhinitis	533	70.2	11	57.9	0.26
Headache	113	16.4	2	12.5	0.67
Sore throat	193	27.5	2	11.8	0.12
Cough	454	60.1	8	42.1	0.12
Stomachache	106	14.5	1	5.3	0.20
Diarrhoea	58	7.7	0	0.0	
Fever and cough	96	12.6	3	15.8	0.69
Fever, cough and rhinitis	78	10.2	3	15.8	0.46

TABLE 2 Symptoms reported by caregiver, by positivity in SARS-CoV-2 PCR test

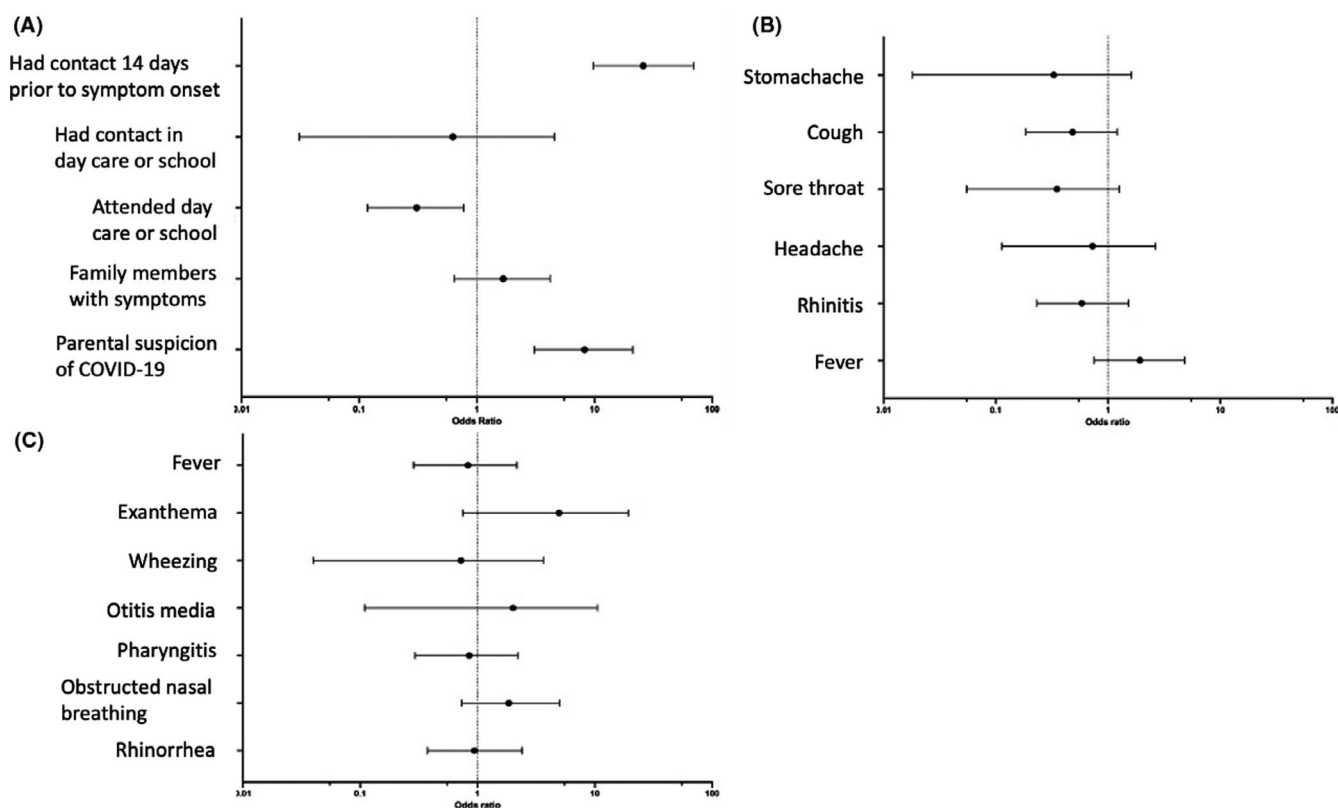


FIGURE 1 Odds ratios and 95% confidence intervals for (A) exposures to SARS-CoV-2 and parental suspicion of COVID-19 as reported by the caregiver and testing positive for SARS-CoV-2, (B) symptoms reported by the caregiver and (C) findings on the physical examination

The exposure history showed a significant correlation between recent exposure to a case of COVID-19 (Odds ratio 25.9, 95% CI: 9.78–70.00, $p < 0.0001$) and a negative and significant correlation with an attendance of day care or school ($p = 0.01$; Table 3; Figure 1A). Parental suspicion that the child may be infected with SARS-CoV-2 was correlated with testing positive for SARS-CoV-2 (p -value < 0.0001 ; Figure 1A). However, no child in which the parents suspected an infection with SARS-CoV-2 was infected with the virus when there had not been a known recent exposure.

3.4 | Analysis of key mutations of SARS-CoV-2

The analysis for key mutations of the SARS-CoV-2 variant of concern Alpha was successful in 13 of the 19 positive samples. The viral load was too low for successful testing in six. The presence of both the mutation N501Y and del69/70 suggests the presence of the Alpha variant in eight samples, and the absence of these mutations suggested that Alpha was not present in five samples. For samples with likely presence of the variant Alpha, the mean Ct value was 20.06

TABLE 3 Findings on clinical examination, by positivity in SARS-CoV-2 PCR test

Findings on clinical examination	SARS-CoV-2 negative		SARS-CoV-2 positive		p value
	Symptom present (n)	(%)	Symptom present (n)	(%)	
Rhinorrhoea	408	54.2	10	52.6	0.89
Obstructed nasal breathing	362	48.1	12	63.2	0.19
Pharyngitis	278	37.1	6	33.3	0.74
Tonsillitis	38	5.1	0	0.0	
Otitis media	24	3.2	1	6.3	0.55
Dyspnoea	18	2.4	0	0.0	
Crackles	39	5.2	0	0.0	
Wheezing	60	8.0	1	5.9	0.74
Rash	19	2.6	2	11.8	0.09
Fever	206	35.0	6	31.6	0.71

TABLE 4 Exposure history, by positivity in SARS-CoV-2 PCR test

Exposure	SARS-CoV-2 negative		SARS-CoV-2 positive		p-value
	n	%	n	%	
Attending day care or school within 10 days prior to symptom onset	536	70.3	8	42.1	0.01
Contact with a known case of COVID-19 14 days prior to symptom onset	30	4.1	10	52.6	<0.0001
Contact to a known case of COVID-19 in day care	20	28.6	1	20.0	0.67
Family member with symptoms of COVID-19	220	30.3	8	42.1	0.28
Parental suspicion	56	8.1	8	42.1	<0.0001

(range 16.3–28.7). The mean Ct value for non-Alpha samples was 23.14 (range 20.2–28.6), when targeting the ORF-1 region of SARS-CoV-2. The difference is not statistically significant ($p = 0.1904$).

4 | DISCUSSION

In our study of 783 children with symptoms of an acute infection seeking consultation from a primary-care paediatrician, the majority had no evidence of an infection with SARS-CoV-2. SARS-CoV-2 was the probable cause of the presented symptoms in 2.4% of children in our study (95% CI: 1.5%–3.8%). The median age of children with evidence of an infection with SARS-CoV-2 was 3 years and 0 months. This reflects the low age of the children who participated in the study with the same median age. This is likely because older children less commonly consult a paediatrician for mild symptoms of an airway infection than younger age groups. It should not suggest that older children are less likely to be tested positive. The clinical severity of the disease was mild in all children with a SARS-CoV-2 infection throughout the study.

When examining both the symptoms reported by the parents and the findings determined by the paediatricians, there were no discernible differences between the symptomatology of children with COVID-19 and those with other causes of an acute infection. The presence of common symptoms of COVID-19, such as cough and

fever, did not significantly increase the probability of testing positive for SARS-CoV-2 when compared with all children in the study. The most prevalent symptoms in the children with evidence of SARS-CoV-2 were also the most prevalent symptoms among the children without evidence of an infection with this virus, which were fever, rhinitis and cough. These symptoms were also most prevalent in another community-based study of children up to the age of 18 years with COVID-19.⁵ In our study, no child with a SARS-CoV-2 infection had diarrhoea, and stomach ache was rare (Table 2), but gastrointestinal symptoms were also less prevalent than respiratory symptoms in all children. In contrast to a community-based study from Canada, we did not observe a correlation between testing positive for SARS-CoV-2 and the gastrointestinal symptoms or fever.⁵ This may be due to the small number of children with COVID-19 in our study, and the local and seasonal prevalence of other respiratory and gastrointestinal pathogens.

Dysgeusia is strongly associated with COVID-19 in adolescents and adults,^{5,8} but cannot be easily assessed in young children. It was therefore not examined in this study that examined children with a median age of 3 years.

As expected, there was a strong positive correlation with having had contact with a known case of COVID-19. Having attended day care or school in the 10 days before symptom onset was significantly and reversely associated with testing positive for SARS-CoV-2 in our study ($p = 0.01$; Table 4, Figure 1). Having had contact with a known

case of COVID-19 in day care or school was not significantly correlated with testing positive for SARS-CoV-2.

We do not believe that the case numbers in our study were large enough to establish that attending day care or school were a factor that made testing positive for SARS-CoV-2 less likely. Importantly, the median age (3 years, 0 months) was too low to allow conclusions on the risk of attending school. However, we could also not identify having visited day care or school as a strong risk factor for testing positive for SARS-CoV-2 in this study of children with symptoms of an acute infection. In another study, having visited in-person schooling was also not associated with testing positive for SARS-CoV-2.⁷ However, the emergence of more transmissible variants of SARS-CoV-2, such as the Delta variant, may change transmission dynamics in the educational setting in the future.

There was a significant correlation between parents suspecting that the child may be infected with SARS-CoV-2 and the detection of the virus ($p < 0.0001$). However, no child tested positive when the parents suspected an infection but there had not been a known contact with a case of COVID-19. Out of 64 cases where the parents suspected an infection with SARS-CoV-2, only 8 were indeed infected (Table 4).

During the study period, the variant of concern Alpha, also known as B.1.1.7, became the dominant strain in Germany.⁹ This rise in the rate of infections caused by this variant can also be observed in our study cohort. Samples in which key mutations suggested the presence of the variant Alpha had higher median viral load than the 'original variant'. However, the number of samples that tested positive for the Alpha variant was not large enough to allow any conclusions on the variant-distinct viral loads or the clinical presentation.

In surveillance reports, influenza has been largely absent as the causative agent for respiratory tract infections during the common season of infection surges in 2020/2021.¹⁰ Accordingly, none of the children in our study had evidence of an infection with influenza A or B. The general activity of acute respiratory tract infections during the study period was also considerably lower when compared with the years before,¹⁰ with the strongest decline among children below the age of 14 years of age. This is likely attributable to non-pharmaceutical interventions targeting the spread of SARS-CoV-2.¹¹

There are some limitations of our study. Foremost, the low number cases of COVID-19 in the study caused uncertainty in the statistical evaluation of associated factors. The case numbers among different age groups were not large enough to draw distinctive conclusions on the presentation in different age groups. Due to voluntary participation in the study and not all children with similar symptoms seeking medical care, the makeup of the study population may not reflect a representative sample of children with acute infections. Some symptoms are not applicable to all age groups but were analysed together. No asymptomatic children were tested for SARS-CoV-2, despite the common occurrence of asymptomatic infections with SARS-CoV-2 in childhood. Furthermore, we examined mid-turbinated nasal swabs instead of nasopharyngeal swabs to minimise the discomfort to the children. This may have influenced testing sensitivity. Previous comparative studies have demonstrated

the mid-turbinate nasal swab, compared to the nasopharyngeal¹² and oropharyngeal swabs,¹³ to be a viable material, especially in the early phase of an infection with SARS-CoV-2.¹⁴

In conclusion, the findings of our study demonstrate that COVID-19 among children with signs of an acute infection could not be easily distinguished from other causes, as the most prevalent symptoms overlapped.

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CONFLICT OF INTERESTS

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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