

# Novel coronavirus infection (COVID-19) in children younger than one year: A systematic review of symptoms, management and outcomes

Ali Ahmed Raba<sup>1,2</sup>  | Anis Abobaker<sup>3</sup> | Ismail Suliman Elgenaidi<sup>4</sup> | Ahmed Daoud<sup>5</sup>

<sup>1</sup>School of Medicine and Medical Sciences, University College Dublin (UCD), Dublin, Ireland

<sup>2</sup>Department of Paediatrics, Coombe Women and Infants University Hospital, Dublin, Ireland

<sup>3</sup>Spire Fylde Coast Hospital, Blackpool, UK

<sup>4</sup>School of Medicine, Trinity College Dublin, Trinity Translational Medicine Institute, Dublin, Ireland

<sup>5</sup>Department of Paediatrics and Neonatology, Portiuncula University Hospital, Ballinasloe, Ireland

## Correspondence

Ali Ahmed Raba, Coombe Women and Infants University Hospital, Dublin 8, Dublin, Ireland.  
Email: ali.raba@ucdconnect.ie

## Abstract

**Aim:** The aim of this systematic review was to evaluate the clinical characteristics of COVID-19 in neonates and children under one year of age.

**Methods:** A systematic literature review of the MEDLINE, PubMed, CINAHL, Embase and EBSCO databases was carried out for studies from January 1, 2020, to April 7, 2020. We included all papers that addressed clinical manifestations, laboratory results, imaging findings and outcomes in infants and neonates.

**Results:** Our search identified 77 peer-reviewed papers, and 18 papers covering 160 infants were reviewed. One paper was from Vietnam, and the other 17 were from China: eight were cross-sectional studies, eight were case reports, one was a case series, and one was a prospective cohort study. The most common clinical symptoms were fever (54%) and cough (33%). Most infants were treated symptomatically, with frequent use of various empirical medications. Infants and neonates tended to have more severe COVID-19 disease than older children: 11 (7%) were admitted to intensive care and one infant died. The mortality rate was 0.006%, with favourable outcomes in most cases.

**Conclusion:** Infants and neonates were more vulnerable to more severe COVID-19 disease than older children, but morbidity and mortality were low.

## KEYWORDS

clinical characteristics, infants, neonates, novel coronavirus, outcomes

## 1 | INTRODUCTION

Since the initial outbreak in China in December 2019, COVID-19, which is caused by severe acute respiratory syndrome 2 (SARS-CoV-2), has spread worldwide. It was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020.<sup>1</sup>

The incidence of COVID-19 is lower in children than adults.<sup>2</sup> Based on the results of 45 scientific papers published up to March

18, 2020, the numbers of children diagnosed with COVID-19 represented <5% of the total confirmed cases.<sup>3</sup> In addition, young children have tended to develop milder diseases than adults<sup>4</sup> and mortality is rare.<sup>3</sup> Infants are a particularly vulnerable group, they are more likely to suffer critical illness,<sup>4</sup> and they are also more likely to have atypical presentations than older children.<sup>5</sup> As we have scarce information on the symptoms, diagnosis, treatment and outcomes of COVID-19 in the paediatric population, we conducted this

**Abbreviations:** COVID-19, coronavirus disease 2019; CT, computed tomography; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

The authors are equal in contribution to this review.

systematic review to collect comprehensive clinical data of neonates and infants with confirmed COVID-19. This included the proportion of patients requiring hospital and intensive care unit (ICU) admission.

## 2 | METHODS

### 2.1 | Literature sources and search strategy

We conducted a systematic review of papers using MEDLINE, PubMed, CINAHL, Embase and EBSCO. The following search terms were used: 'coronavirus' 'nCoV' or '2019-nCoV' or 'SARS-CoV-2' or 'COVID-19' and 'infant' or 'neonate' or 'newborn' or 'newborn infant' or 'child' or 'paediatric' or 'children'. Additional papers were retrieved by screening the reference lists of the included studies. The searches were concluded by April 7, 2020, and four different researchers (AR, AA, IE, AD) independently evaluated the search results.

### 2.2 | Eligibility criteria

We included published peer-reviewed papers that reported cases with demographical, clinical, laboratory and image features of SARS-CoV-2 infections confirmed by real-time reverse transcriptase polymerase chain reaction in infants and neonates. Different study designs, such as cross-sectional, cohort, case-control, case report and case series, were included to assess clinical, laboratory and imaging characteristics. We included publications from January 1, 2020, to April 7, 2020. Narrative review papers, and letters that did not present original data

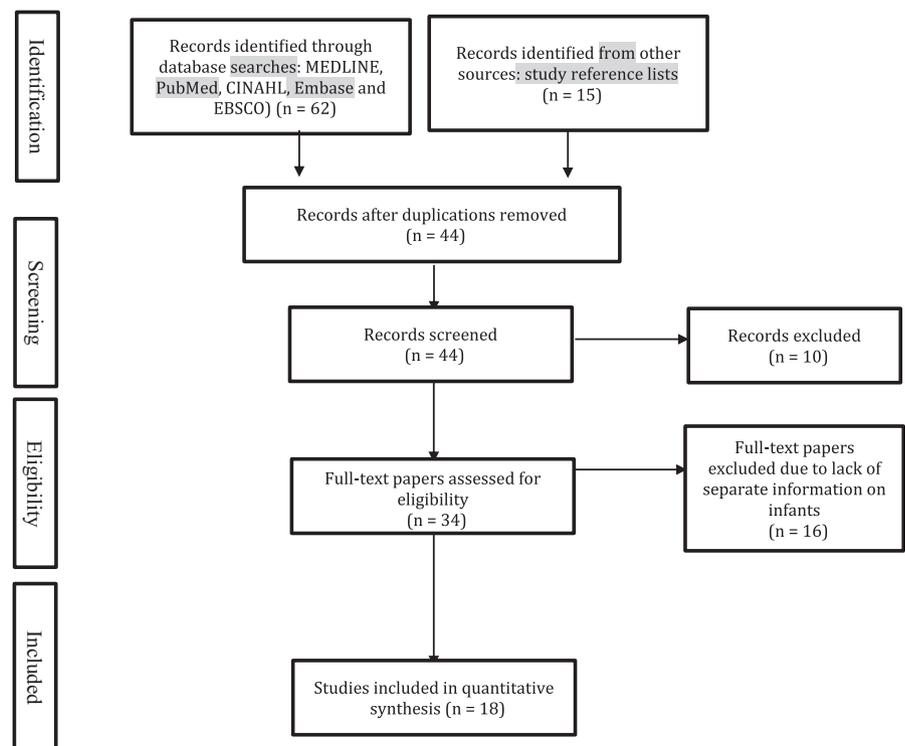
### Key Notes

- This systematic review investigated the clinical features, management and outcome of 160 neonates and infants with COVID-19.
- The most common clinical symptoms identified by the 18 papers from China and Vietnam were fever (54%) and cough (33%).
- Infants were more vulnerable to severe disease than older children, but COVID-19 was associated with low morbidity and mortality in this age group.

were excluded, as well as studies reporting cases with incomplete information.

### 2.3 | Study selection

The database files were extracted using Zotero reference management software version 5.0.87 (George Mason University, Virginia, USA), and results of the initial search strategy were initially screened by title and abstract. Full texts of these screened papers were examined for inclusion and exclusion criteria for the systematic review (Figure 1). When a paper reported duplicate information on the same patient, the information from both reports was combined in order to obtain complete data. However, they only counted as a single case.



**FIGURE 1** PRISMA flow diagram showing study selection process

**TABLE 1** Characteristics of the included studies

Author	Country	Journal	Date (DD/MM/YY)	Study type	Total number of children	Number of infants
Wei et al <sup>7</sup>	China	JAMA	14/02/2020	Cross-sectional	9	9
Zhang et al <sup>24</sup>	China	CJCP	26/02/2020	Case report	2	2
Tian et al <sup>25</sup>	China	J Infect	27/02/2020	Cross-sectional	262	3
Zhou et al <sup>22</sup>	China	CJCP	27/02/2020	Cross-sectional	9	5
Wang et al <sup>10</sup>	China	CJCP	27/02/2020	Case report	1	1
Cai et al <sup>26</sup>	China	Clin Infect Dis	28/02/2020	Case series	10	2
Kam et al <sup>27</sup>	China	Clin Infect Dis	28/02/2020	Case report	1	1
Li et al <sup>28</sup>	China	Korean J Radio	05/03/2020	Case report	2	1
Xia et al <sup>29</sup>	China	Pediatr Pulmonol	05/03/2020	Cross-sectional	20	9
Liu et al <sup>21</sup>	China	N Engl J Med	12/03/2020	Cross-sectional	6	1
Su et al <sup>20</sup>	China	Emerg Microbes Infect	12/03/2020	Cross-sectional	9	2
Wang et al <sup>11</sup>	China	Clin Infect Dis	12/03/2020	Case report	1	1
Dong et al <sup>4</sup>	China	Pediatrics	16/03/2020	Cross-sectional	731	86
Cui et al <sup>30</sup>	China	J Infect Dis	17/03/2020	Case report	1	1
Lu et al <sup>8</sup>	China	N Engl J Med	18/03/2020	Cross-sectional	171	31
Le et al <sup>31</sup>	Vietnam	Lancet Child Adolesc Health	23/03/2020	Case report	1	1
Liu et al <sup>32</sup>	China	JCAT	25/03/2020	Case report	5	1
Zeng et al <sup>9</sup>	China	JAMA pediatr	26/03/2020	Cohort study	33	3

## 2.4 | Data collection and data items

Data collection forms were independently completed by two investigators (IE, AA). These included information on the authors, the title, type, year and date of publication, the number of reported cases and their age and gender. The form recorded clinical features, like cough, fever, sore throat, dyspnoea and gastrointestinal symptoms and management and outcome, such as oxygenation, ICU admission, ventilation and death. The laboratory findings included white blood cell counts, lymphocytes, C-reactive protein, liver function tests and renal function tests and the imaging section included chest X-rays and chest computed tomography (CT) scans. A third researcher (AR) checked the paper list and data extractions to ensure there were no duplicate papers or duplicate information on the same patient. That researchers also any resolved discrepancies about the study inclusion.

## 2.5 | Risk of bias and statistical approach

The quality of the included studies was independently rated by two reviewers using the National Institutes of Health Quality Assessment Tool of systematic reviews and meta-analysis<sup>6</sup> (Table 1).

All units were converted to standard measurements for that variable to resolve any unit discordance. Percentages and means were calculated to describe the distributions of categorical and continuous variables, respectively. The baseline data were

analysed using the SPSS version 24 for Windows (IBM Corp, New York, USA).

## 3 | RESULTS

A total of 77 records were retrieved using the search strategy. After we eliminated the duplicate records and reviewed the abstracts and titles, 44 records were deemed relevant. We excluded 10 papers due to lack of information on the molecular diagnosis. The remaining 34 full-text papers were assessed for eligibility, and 16 were excluded due to lack of information on children younger than one year in their samples. This meant that 18 papers covering 160 infants were included in the final review. All the included studies were from China, except for one case report from Vietnam. Eight studies were cross-sectional, eight were case reports, one was a case series, and one was a prospective cohort study. The largest study in our review was a report from China conducted by Dong et al,<sup>4</sup> which comprised included 86 infants with confirmed COVID-19. The characteristics of the included studies are presented in Table 1.

### 3.1 | Demographic characteristics

A total of 160 infants with confirmed COVID-19, including five neonates, were studied. The mean age of the patients was 5.9 months old (range one day to 12 months), and 59% were females, with a female to male ratio of 1.4:1.

### 3.2 | Clinical manifestations, laboratory and imaging findings

Clinical symptoms and laboratory parameters in the overall population are reported in Tables 2 and 3. These show that 16% of infants were asymptomatic, including one neonate born to a mother with COVID-19. The most common symptoms were fever (54%), followed by cough (33%), rhinorrhoea (23%), gastrointestinal symptoms (16%) and dyspnoea (3%). A study of nine infants with confirmed COVID-19 revealed that four cases presented with fever, two had mild upper respiratory tract symptoms, one was asymptomatic, and two infants had no available information on symptoms.<sup>7</sup>

The laboratory results were contrary to reports in adults: lymphocytosis (61%) was the most prevalent laboratory finding, followed by abnormal liver function tests (54%), high C-reactive protein (47%), lymphopenia (16%) and abnormal renal function tests (11%). The majority of the included studies did not report whether chest CT scans were performed or not. Chest CT was reported only in 12% of infants and 84% of these scans were abnormal. The most commonly reported finding was ground-glass opacity with progression to consolidation.

### 3.3 | ICU admission and outcomes

Although all the included infants were admitted to hospitals, only 11 (7%) infants required ICU admission. Of those, three were ventilated.

A study from China<sup>7</sup> of nine infants reported that no infant required ICU admission, mechanical ventilation or had any severe complications. One death was reported in one study,<sup>8</sup> a 10-month-old infant with intussusception complicated by multiorgan failure, who died four weeks after admission. Another study<sup>4</sup> reported that 33 infants had severe infections and seven infants were critically ill. However, no infant died in their sample.

### 3.4 | Management and treatment

A wide variety of management strategies for infants with COVID-19 were reported in the included studies. Most studies reported supportive treatment as the mainstay of management for cases with severe COVID-19. Half of the included infants did not receive any specific medication. The other half received medications: 48% were given interferon, 36% antibiotics, 8% steroids and 7% received immunoglobulin.

### 3.5 | Neonates

There were five neonates aged <28 days with confirmed COVID-19 who were reported in three studies.<sup>9-11</sup> Of those, four neonates were born by Caesarean delivery to mothers with COVID-19 and nasopharyngeal and anal swabs were positive for SARS-CoV-2 within 48 hours of life. Three neonates were born at term, and one was born prematurely at 31 weeks and two days of gestation and required admission to the ICU and ventilation. Another neonate was tested positive for SARS-CoV-2

**TABLE 2** Clinical manifestations

Author	N	Fever	Cough	Rhinorrhoea	Dyspnoea	GI symptoms	ICU	Death
Wei et al <sup>7</sup>	9	4 (44%)	2 (22%)	1 (11%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Zhang et al <sup>24</sup>	2	1 (50%)	2 (100%)	2 (100%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)
Tian et al <sup>25</sup>	3	—	—	—	—	—	0 (0%)	0 (0%)
Zhou et al <sup>22</sup>	5	3 (60%)	2 (40%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Wang et al <sup>10</sup>	1	1 (100%)	1 (100%)	—	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Cai et al <sup>26</sup>	2	1 (50%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Kam et al <sup>27</sup>	1	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Li et al <sup>28</sup>	1	1 (100%)	—	—	—	—	—	0 (0%)
Xia et al <sup>29</sup>	9	—	—	—	—	—	—	0 (0%)
Liu et al <sup>21</sup>	1	1 (100%)	0 (0%)	NA	NA	NA	0 (0%)	0 (0%)
Su et al <sup>20</sup>	2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Wang et al <sup>11</sup>	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (100%)	0 (0%)
Dong et al <sup>4</sup>	86	—	—	—	—	—	7 (8%)	0 (%)
Cui et al <sup>30</sup>	1	1 (100%)	1 (100%)	1 (100%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Lu et al <sup>8</sup>	31	—	—	—	—	—	—	1 (3%)
Le et al <sup>31</sup>	1	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Liu et al <sup>32</sup>	1	1 (100%)	1 (100%)	—	—	—	—	0 (10%)
Zeng et al <sup>9</sup>	3	2 (66%)	0 (0%)	0 (0%)	1 (33%)	2 (66%)	2 (66%)	0 (0%)

Abbreviations: GI, gastrointestinal; ICU, intensive care unit.

TABLE 3 Laboratory findings, imaging and management

Author	N	Lymphopenia	Lymphocytosis	Abnormal LFTs	High CRP	Abnormal RFTs	Chest xray	Chest CT	Management
Wei et al <sup>7</sup>	9	–	–	–	–	–	–	–	–
Zhang et al <sup>24</sup>	2	0 (0%)	2 (100%)	2 (100%)	2 (100%)	0 (0%)	–	2 (100%)	IV immunoglobulin: 1 (50%) recombinant human IFN- $\alpha$ 2: 2 (100%)
Tian et al <sup>25</sup>	3	–	–	–	–	–	–	–	–
Zhou et al <sup>22</sup>	5	0 (0%)	5 (100%)	–	3 (60%)	–	–	5 (100%)	Inhaled interferon: 5 (100%) oral ritonavir: 5 (100%)
Wang et al <sup>10</sup>	1	0 (0%)	0 (0%)	–	0 (0%)	–	–	1 (100%)	Inhaled Interferon: 1 (100%) Fluid replacement: 1 (100%)
Cai et al <sup>26</sup>	2	0 (0%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	1 (50%) Abnormal	–	Supportive: 2 (100%) antibiotics: 2 (100%) antivirals: 0 (0%) steroids: 1 (50%)
Kam et al <sup>27</sup>	1	0 (0%)	0 (0%)	0 (0%)	–	–	–	–	Supportive: 0 (0%) antibiotics: 0 (0%) antivirals: 0 (0%) steroids: 0 (0%)
Li et al <sup>28</sup>	1	0 (0%)	1 (100%)	–	1 (100%)	–	–	1 (100%) Abnormal	–
Liu et al <sup>21</sup>	1	–	–	–	–	–	–	1 (100%) Abnormal	Supportive: 1 (100%) antibiotics: 1 (100%) antivirals: 1 (100%) steroids: 1 (100%)
Su et al <sup>20</sup>	2	0 (0%)	1 (50%)	–	0 (0%)	–	–	2 (100%) abnormal	Inhaled interferon: 2 (100%) ribavirin: 1 (50%)
Wang et al <sup>11</sup>	1	1 (100%)	0 (0%)	1 (100%)	0 (0%)	–	–	1 (100%) abnormal	Intravenous penicillin G: 1 (100%)
Dong et al <sup>4</sup>	86	–	–	–	–	–	–	–	–
Cui et al <sup>30</sup>	1	0 (0%)	1 (100%)	1 (100%)	0 (0%)	0 (0%)	–	1 (100%)	Inhaled interferon $\alpha$ -1b, amoxicillin potassium clavulanate, reduced glutathione, ursodeoxycholic acid and traditional Chinese medicine
Le et al <sup>31</sup>	1	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%) abnormal	NA	Supportive: 1 (100%) antibiotics: 1 (100%) antivirals: 0 (0%)
Liu et al <sup>32</sup>	1	0 (0%)	0 (0%)	–	–	–	–	1 (100%)	Interferon: 1 (100%)
Zeng et al <sup>12</sup>	3	2 (66%)	0 (0%)	1 (33%)	–	–	3 (100%) abnormal	1 (33%) abnormal	Supportive: 1 (33%) antibiotics: 1 (33%) antivirals: 0 (0%) steroids: 0 (0%)

Abbreviations: CRP, C-reactive protein; CT, computed tomography; IFN- $\alpha$ 2, interferon  $\alpha$ 2; LFTs, liver function tests; RFTs, renal function tests.

on day 22 of life. Their first symptoms were vomiting and refusing milk and they had a history of recent admissions to hospital. The five neonates had pneumonia-like pictures on their chest X-rays and CT scans. No death was reported among this age group.

## 4 | DISCUSSION

This systematic review was performed to identify the key clinical, laboratory and imaging findings, as well as the management and outcomes, of COVID-19 in infants and neonates.

It is common for children, especially infants, to harbour and shed infectious organisms, particularly respiratory viruses, even when they are asymptomatic.<sup>12</sup> During the current COVID-19 pandemic, concerns have been raised regarding the role of asymptomatic young children in the transmission of infection and this poses a significant infection control challenge.<sup>13</sup> However, because of the limited data on infants with COVID-19, the contribution of asymptomatic younger children to the transmission of this virus is not well reported.

Our systematic review showed that the most common presenting symptoms in infants with COVID-19 were fever and cough. However, some infants only had fever, unlike the usual combination of fever and cough in older children and adolescents.<sup>5</sup> Other less common symptoms included upper respiratory tract symptoms and gastrointestinal symptoms. We also noted that 16% were asymptomatic. In general, children with COVID-19 develop mild forms of the disease,<sup>3</sup> but infants are more vulnerable to acquiring the SARS-CoV-2 infection.<sup>4</sup> A retrospective study conducted by Dong et al,<sup>4</sup> which included the largest number of infants in our review, revealed that 10.6% of the 86 infants had severe and critical illness compared with only 4.1% of children aged 11-15 years. This could be because the immune system structure and functioning in infants are less mature in comparison with older children. Compared with infants, the percentage of severe and critical disease in adults is much higher (18.5%).<sup>4</sup> This might be explained by the fact that infants are exposed to more frequent viral infections than adults, which trains their immune system to deal with SARS-CoV-2 infection more effectively.<sup>3</sup> Another theory that explains milder disease in infants and children is angiotensin-converting enzymes 2 receptors, which are the binding site for the SARS-CoV-2 virus.<sup>14</sup> These are less mature in children than adults.<sup>3</sup> Furthermore, the fact that the immune system in infants is not yet fully developed means that they are unable to mount a cytokine storm, which is responsible for the disease severity seen in adults.<sup>2</sup> In summary, children younger than 16 years with COVID-19 develop mild symptoms and disease. However, infants are more vulnerable to more severe disease than older children.

Our review found that the most common laboratory abnormalities in infants with COVID-19 were lymphocytosis. Lymphopenia was less commonly reported in infants, which is contrary to what has been reported in adult patients. Henry et al summarised the laboratory results of 12 studies, which comprised 66 children aged from

six weeks to 17 years.<sup>15</sup> The results showed that only 3% had lymphopenia. In another study, of 171 children aged between one day and 15 years, lymphopenia was only present in six patients (3.5%).<sup>8</sup> On the other hand, another study found that out of 1099 adult patients with confirmed COVID-19, 83.2% had lymphopenia on admission.<sup>16</sup> Other studies showed that lymphopenia was reported in 85% of critically ill adult patients with COVID-19,<sup>17</sup> whereas only 25% of adults with mild disease had lymphopenia.<sup>15</sup> This might indicate that lymphopenia correlates with the severity of the disease. The absence of significant lymphopenia in infants and children could be explained by their milder illness, as lymphopenia is more common in severe disease.<sup>3</sup> The other possible explanation is that the immune systems of infants and children are less mature than adults and they respond differently to viral infection.<sup>15</sup>

Unfortunately, most of the studies included in this review did not report whether chest CT scans were performed or not for infants admitted to hospitals. Chest CT scans were only reported in 12% of infants, and the most common finding was ground-glass opacity with progression to consolidation. The chest CT findings in infants were somewhat similar to the findings in adults. The most common CT findings in adult patients have been patchy ground-glass opacity with bilateral involvement and sub-pleural peripheral distribution commonly involving the lower lobes.<sup>18</sup> Interestingly, one study reported that chest CT scans were normal in adult patients with mild disease.<sup>19</sup> Giving the mild nature of the disease in infants, this could explain why chest CT scan findings were under-reported in most of the studies included in this review.

After reviewing the included studies, there was no specific protocol for managing infants with COVID-19 and most of the treatment plans were decided according to local hospital guidelines. However, it has been reported in the literature that antibiotics, antivirals, steroids, inhaled interferon and immunoglobulin have been used to treat COVID-19. The most commonly used antibiotics in our review were amoxicillin, azithromycin and penicillin G. Antiviral agents, such as ribavirin and oseltamivir, were also tried as potential treatment options.<sup>20,21</sup> A retrospective analysis conducted by Zhou et al<sup>22</sup> comprised five infants with COVID-19. All the patients received oral ritonavir and inhaled interferon, and none of them received antibiotics. Zeng et al<sup>9</sup> reported that one out of three neonates with confirmed SARS-CoV-2 infections was started on antibiotics, based on their clinical condition, laboratory findings and imaging features. We found that infants with respiratory distress were managed by supplementary oxygen and very rarely required mechanical ventilation.

It has been suggested that chloroquine exhibits some antiviral activity and it might relieve the symptoms of acute respiratory distress syndrome in adults with COVID-19. However, chloroquine was not seen as a treatment option in our review.

Our review showed that the prognosis for COVID-19 in children younger than one year was favourable, in comparison with older age groups. The reviewed studies reported one death, a 10-month-old child with intussusception and multiorgan failure,<sup>8</sup> which could constitute a very low mortality rate (0.006%) in this age group. This

cannot be compared to the figures from most adult studies, where mortality rates ranged between 1% and 5%.<sup>23</sup> That is because the presence of one or more comorbidities is more prevalent among older age groups and could be a detrimental factor in the clinical outcomes.

The number of available studies on COVID-19 in infants and newborn infants is small, and they are limited in terms of data availability. We acknowledge that the few larger studies included in our review were conducted on different paediatric age groups. Therefore, there were no separate demographic and clinical characteristics for infants. However, they were included in our review, as we were able to extract some data on infants, such as mortality and outcomes, from those studies and that added significant information to the limited literature on this group of children. In addition, although our search was comprehensive and there is no evidence that studies that met the inclusion criteria were missed, it is still possible. That this might have had an impact on our final results.

## 5 | CONCLUSION

The existing literature demonstrates that infants and neonates with COVID-19 were slightly susceptible to severe disease, compared with older children. However, it was associated with low morbidity and mortality in this age group. The symptoms of young children with COVID-19 were diverse. The main symptoms were fever and cough, and some children were asymptomatic. Our analysis demonstrated that lymphocytosis was the most prevalent laboratory abnormality in infants with COVID-19. Evidence is accumulating rapidly, so these data may need to be updated soon.

## CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

## ORCID

Ali Ahmed Raba  <https://orcid.org/0000-0003-2133-319X>

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**How to cite this article:** Raba AA, Abobaker A, Elgenaidi IS, Daoud A. Novel coronavirus infection (COVID-19) in children younger than one year: A systematic review of symptoms, management and outcomes. *Acta Paediatr*. 2020;109:1948-1955. <https://doi.org/10.1111/apa.15422>