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Evidence summary for natural history of COVID-19 in children

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The Health Information and Quality Authority (HIQA) has developed a series of 'Evidence summaries' to assist the Clinical Expert Advisory Group (EAG) in supporting the National Public Health Emergency Team (NPHE) in their response to COVID-19. These summaries are based on specific research questions.

This evidence summary was developed to address the following research question:

What is the natural history of COVID-19 in children?

The processes as outlined in HIQA's protocol (available on www.hiqa.ie) were followed. Relevant databases of published literature and pre-print servers were searched. Below is the summary of the evidence published between 30 December 2019 and 19 March 2020 identified as relevant to this review question. Data published by national agencies are not included.

Results

A total of 12 studies were identified and included in this summary (Table 1). Four studies comprised case reports,⁽¹⁻⁴⁾ six were case series,⁽⁵⁻¹⁰⁾ one was an analysis of a crowd-sharing database from social media sources,⁽¹¹⁾ and one describes a decision-tree that classifies paediatric patients as 'severe' or 'mild' for early diagnosis and intervention.⁽¹²⁾

The case reports, case series and decision-tree were all based on data from China. The analysis of the crowd-sharing online database comprised 46.3% data from China, with the rest originating in other countries.

Presenting symptoms

In general, fever and cough appear to be the most common presenting symptoms in children, as well as fatigue, gastro-intestinal symptoms (abdominal discomfort, nausea, vomiting, abdominal pain, diarrhoea), upper respiratory tract infections (URTIs) (pharyngeal erythema, nasal congestion, runny nose), with lower RTIs rarely occurring. Adult manifestations of acute respiratory distress syndrome (ARDS), and acute lung injury⁽⁵⁾ appear to be rare in children, even in those whose chest X-ray and CT show pneumonia.⁽⁵⁾ Yu, Cai⁽⁷⁾ described most of the 82 children in their study as having mild symptoms, although chest X-ray and CT showed that 30 had bilateral pneumonia, 38 unilateral pneumonia and 30 myocardial damage.

Of the four case reports, two describe infants,^(1, 4) one a seven year old child,⁽²⁾ while the age of the fourth child is unclear.⁽³⁾ The children's presenting symptoms were largely consistent with the case series reported above. Of note is a 'critically ill'

child who rapidly progressed to acute respiratory distress syndrome, sepsis and acute kidney failure, although on presentation there were no obvious respiratory symptoms and two negative pharyngeal swabs.⁽³⁾ It is unclear whether this child recovered, although the Chinese CDC⁽⁹⁾ report that there have been no deaths in those aged less than nine years.

Incubation period and viral shedding

The incubation of COVID-19 may be longer in children than in adults and viral shedding in respiratory and stool specimens may occur for longer in children than in adults.⁽¹¹⁾ One study found that while a recovering infant's pharyngeal swabs tested negative 10 days after admission, anal swabs were still positive, but were found to be negative when tested on day 26.⁽¹⁾ Xing et al.⁽⁶⁾ found that clearance of viral RNA in respiratory tract occurred within two weeks after abatement of fever; however, it remained positive in stools of paediatric patients for longer than four weeks. In two children faecal swabs turned negative 20 days after throat swabs had tested negative, while that of another child lagged behind for 8 days. Tang et al.⁽⁵⁾ found that nasal and anal swabs can test positive even without respiratory or gastrointestinal symptoms. In contrast, Chen et al.⁽³⁾ report that, for a critically ill child, two early pharyngeal swabs were negative for COVID-19.

Length of hospital stay

Two studies of 26 and 82 children reported on length of hospital stay, finding that children were discharged on average after 13.6 days (+/- 1.0 days),⁽⁵⁾ and 11.2 days,⁽⁷⁾ respectively.

Clinical management

Five studies report on the clinical management of children,^(1, 4-7) three describing the treatment of single patients^(1, 4) or small groups of patients⁽⁶⁾ and two, the treatment of 26 and 82 children, respectively.^(5, 7) One study⁽⁶⁾ reports a 'good response to supportive treatment' in three children, but does not specify which treatment could be considered curative. One study⁽⁵⁾ describes treatment with interferon and antiviral agents, despite no patient having serious complications and or ARDS. Another describes how an asymptomatic neonate was treated with IV penicillin and vitamin K1.⁽⁴⁾ Yu et al.⁽⁷⁾ report how all 82 patients in the study, most of whom were described as having mild clinical symptoms, were treated in isolation with interferon atomisation therapy and most were given antibiotic or antiviral treatment.

Study quality and quality of the evidence

Two case reports were available in Chinese only, the abstracts of which were translated using Google translate.^(2, 3) Six of the included studies have not yet been peer-reviewed and are available as 'pre-prints' only, thus potential inaccuracies or

limitations of the studies may have not yet been detected.^(5-8, 11, 12) It is possible that there is duplication of data between a number of the Chinese case reports and case series, while it is also unclear whether the analysis of crowd-sharing data⁽¹¹⁾ includes data from some of the other studies discussed in this report.

Discussion

This report includes data from studies that are mainly Chinese in origin which, therefore, may not be generalisable to the Irish population. In particular, data on length of stay in hospital or clinical management may be context specific as these data reflect the early stage of the epidemic in China when asymptomatic or mild cases may have been hospitalised until tested negative, rather than being based on clinical need.

Findings on presenting symptoms concur with a recently published discussion paper.⁽¹³⁾ This paper reported that some children are asymptomatic and many have mild symptoms, and recover 1-2 weeks from onset. Serious symptoms such as ARDS, septic shock, refractory metabolic acidosis and coagulation dysfunction are rare in children.⁽¹³⁾

A Chinese Expert Consensus statement reports that clinical findings in infants are non-specific, especially in premature infants, although COVID-19 can be detected in the URT, lower respiratory tract (LRT), bloods and stool and that chest imaging is likely to show pneumonia.⁽¹⁴⁾ Symptoms in infants may include tachypnoea, grunting, nasal flaring, work of breathing, apnoea, cough, tachycardia, poor feeding, lethargy, diarrhoea and abdominal distension. The findings of typically asymptomatic or mild disease course are also consistent with recent epidemiological data published by national agencies in Italy (62,844 diagnosed cases) and Spain (19,980 diagnosed cases), which report no fatalities in children, a low incidence of hospitalisation and a low burden of LRTI.^(15, 16)

Conclusion

In general, the presentation of symptoms in infants and children is variable, although most have mild symptoms and many are asymptomatic. Of note, one study of a critically ill child found that early pharyngeal swabs had tested negative for the virus. Conversely, stool samples can remain positive for COVID-19 several weeks after abatement of symptoms and negative testing of pharyngeal swabs. There is limited data available on hospital length of stay and appropriate clinical management of children.

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Table 1: Characteristics of included studies

Author Country Study design URL	Population setting Patient demographics	Outcome results • Clinical history • Clinical management
<p>Cai et al.</p> <p>China Fudan University Hospital</p> <p>Case report</p> <p>Peer review: Unclear/probably (abstract only - in Chinese)</p> <p>URL:http://rs.yiigle.com/CN112140202002/1182388.htm</p>	<p>Population / setting: 1 patient admitted to hospital</p> <p>Patient demographics: 7-year old child</p>	<p>Clinical history:</p> <ul style="list-style-type: none"> Presented with fever and cough Father positive for Covid-19 <p>Clinical management: Unclear</p>
<p>Chen et al.</p> <p>China</p> <p>Case report</p> <p>Peer review: Unclear/probably (abstract only - in Chinese)</p> <p>URL:http://rs.yiigle.com/CN112140202003/1183493.htm</p>	<p>Population / setting: 1 'critically-ill' child</p> <p>Patient demographics: Male, 13 months old</p>	<p>Clinical history:</p> <ul style="list-style-type: none"> Intermittent diarrhoea and vomiting for 6 days Early respiratory symptoms are not obvious Rapid progress 'ionize' (sic)acute respiratory distress syndrome' Sepsis shock and acute kidney failure 2 early pharyngeal swabs negative for 2019-nCoV nucleic acid <p>Clinical management: Blood volume replenishment immediately after entering the intensive care unit, correction of acidosis, continuous dopamine intravenous injection to improve circulation, and tracheal intubation. Ventilator-assisted ventilation nebulization of interferon α-1b, gamma globulin (400 mg / kg \times 5 d) and methylprednisolone intravenous infusion (2 mg / kg \times 3 d), anti-infection (meropenem, linezolid), Oseltamivir and gastrointestinal decompression. At 9 o'clock on January 27, the child still had no urine and his limbs were cold. Continuous blood purification was performed at 11 o'clock. After treatment, the child's oxygenation was significantly improved on January 29 (PaO₂ / FiO₂ = 212 mmHg, oxygenation index = 7.1). A review of X-rays at the bedside on the 6th day of admission showed improved lung ventilation, lower right lobe and upper left Leaf pneumonia was partially absorbed and right upper lobe atelectasis. On the 10th day after admission, the patient's condition improved significantly.</p>

Author Country Study design URL	Population setting Patient demographics	Outcome results • Clinical history • Clinical management
<p>Cui et al.</p> <p>China, Guizhou Provincial People's Hospital</p> <p>Case report</p> <p>URL:https://doi.org/10.1093/infdis/jiaa113</p>	<p>Population / setting: 1 infant admitted to hospital</p> <p>Patient demographics: 55 day old otherwise healthy female infant</p>	<p>Clinical history:</p> <ul style="list-style-type: none"> • Day 2 to 6 of hospitalisation patient became sicker –progressive pneumonia diagnosed by CT, but good appetite without diarrhoea, oliguria or shock • Lab and CT described in detail • Day 11: stool PCR results positive • Day 10-13: 3 pharyngeal swabs negative • Day 11 and 13: anal swabs still positive • Day 26: anal swabs negative. <p>Clinical management: Inhaled interferon α-1b, amoxicillin potassium clavulanate, reduced glutathione, ursodeoxycholic acid and traditional Chinese medicine lotus qingwen - sputum suctioning, oxygen through nasal cannula and ambroxol, intravenous sodium creatine phosphate.</p>
<p>Henry et al.</p> <p>14 countries (Australia, China, France, Hong Kong, Italy, Japan, Malaysia, Singapore, South Korea, Spain, Switzerland, Thailand, UAE, Vietnam)</p> <p>Secondary analysis of data from open access crowd-sourced databases</p> <p>URL:https://doi.org/10.1101/2020.03.01.20029884</p>	<p>Population/ setting: 82 patients (≤ 19 years) (46.3% Chinese, 53.7% international)</p> <p>Patient demographics:</p> <ul style="list-style-type: none"> • median age 10 – (65.6%) 0-12 yrs – (32.8%)13-19 yrs • males (52.4%); females (32.9%); unknown (14.6%) 	<p>Clinical history: Data only available for 25 patients</p> <ul style="list-style-type: none"> • Fever (68%); Cough (36%); 2 asymptomatic <p>Clinical management: Not reported</p>

Author Country Study design URL	Population setting Patient demographics	Outcome results • Clinical history • Clinical management
<p>Tang et al.</p> <p>China, Shenzhen Center of National Infectious Diseases</p> <p>Retrospective case series</p> <p>URL:https://doi.org/10.1101/2020.03.08.20029710</p>	<p>Population setting: 26 children admitted to hospital</p> <p>Patient demographics: 1yr to 13 yrs -9 males (35%) and 17 females (65%). None of the children had underlying diseases</p>	<p>Clinical history:</p> <ul style="list-style-type: none"> • Asymptomatic (9), fever (11), cough (11), rhinorrhoea (2), diarrhoea (2), vomiting (2), no pulmonary infiltration (8), unilateral pulmonary infiltration (11) and bilateral pulmonary infiltration (7) • No serious complications or ARDS • Detailed lab results reported • Nasal and anal swabs positive even without respiratory symptoms such as vomiting and diarrhoea • 26 patients discharged (13.6 +/- 1.03 days on average) <p>Clinical management:</p> <ul style="list-style-type: none"> • All patients treated in isolation <p>Medicines included oseltamivir, ribavirin, interferon, Kaletra® (lopinavir/ritonavir) and traditional Chinese medicine</p>
<p>Wang et al.</p> <p>China, Wuhan Hospital</p> <p>Case report</p> <p>URL:https://doi.org/10.1093/cid/ci-aa225</p>	<p>Population setting: Neonate admitted to hospital</p> <p>Patient demographics: 36 hour-old male</p>	<p>Clinical history:</p> <ul style="list-style-type: none"> • Emergency C-section – baby had no contact with mother post-partum • Positive pharyngeal swab at 36 hours old • Detailed lab results reported • Day 2 chest X-ray showed thickened lung texture with no abnormalities in heart and palate, but vital signs stable • Cord blood and placenta negative • Mothers breast milk negative • Day 3 chest CT showed high density nodular shadow under pleura of posterior section of upper lobe of right lung • Day 14 few small patches of shadow in upper lobe of right lung remained and anal and pharyngeal swabs were negative <p>Clinical management:</p> <ul style="list-style-type: none"> • Intravenous penicillin, vitamin K1, placed in isolation with no special treatment

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<p>Xing et al.</p> <p>China, Qingdao, Shandong Province</p> <p>Case series</p> <p>URL:https://doi.org/10.1101/2020.03.11.20033159</p>	<p>Population setting: 3 children reported in the province of Qingdao</p> <p>Patient demographics: under 10 yrs-1.5-year-old male; 5-year-old male; 6-year-old female</p>	<p>Clinical history:</p> <ul style="list-style-type: none"> • All presented with fever • Faecal specimens collected in two patients from day 4 of onset and then daily during hospital stay - third patient collected 9 days after hospital discharge • Throat swabs obtained daily during hospital stay and every other day after discharge. • SARS-CoV-2 RNA detected in faeces 8-20 days after negative conversion of viral RNA in respiratory specimens in two patients – unknown in third as child was discharged without faecal testing • None developed severe complications or needed ICU or ventilation • Detailed lab results reported • Chest CT showed delicate patches of ground-glass opacity of lower lobe of left lower lung near pleura in case 1 (day 1) of symptom onset and consolidation changes of left lower lobe near pleura in case 2 on admission - case 3 had no abnormality on CT imaging. <p>Clinical management:</p> <ul style="list-style-type: none"> • Inhalation of interferon, oral ribavirin and traditional Chinese medicine.
<p>Yu et al.</p> <p>China, Wuhan Children's Hospital</p> <p>Case series</p> <p>URL:https://doi.org/10.1101/2020.03.15.20036319</p>	<p>Population setting: 82 children admitted to hospital</p> <p>Patient demographics: 3 days-16 yrs; male 62.2%; female 37.8%;</p>	<p>Clinical history:</p> <ul style="list-style-type: none"> • On admission most had fever or cough – most had mild symptoms and 8 had no symptoms -8 were critically ill –(4 children and 4 infants) • Detailed lab results reported • 30 had myocardial damage • 30, 38 and 18 showed bilateral, unilateral, multiple mottling and ground glass opacity pneumonia respectively. 1 had pleural effusion and 2 had normal chest CTs. <p>Clinical management: All treated in isolation with interferon atomisation therapy. Most given antibiotic or antiviral treatment. 6 received nasal catheter oxygen therapy. 8 transferred to ICU – 3 serious complications. Discharged rate 73.17%. Mean hospital stay was 11.2 days. No deaths.</p>

Author Country Study design URL	Population setting Patient demographics	Outcome results • Clinical history • Clinical management
<p>Yu et al.</p> <p>China, Wuhan Children's Hospital</p> <p>Analysis of the 105 patients to develop a decision-tree that classifies paediatric patients as 'severe' or 'mild' for early diagnosis and intervention</p> <p>URL:https://doi.org/10.1101/2020.03.09.20032219</p>	<p>Population setting: 105 children admitted to hospital</p> <p>Patient demographics: 3 days-16 yrs; male 62.2%; female 37.8%</p>	<p>Clinical history: See above Clinical management: See above</p> <p>Direct Bilirubin (DBIL)<6.1 and Alanine transaminase (ALT)<24.5 in combination were used to identify 8 critically ill paediatric patients compared with 97 other mild patients and 'their combination is revealed as a precise indicator for the severity of COVID-19 paediatric patients'.</p>
<p>Zhang et al.</p> <p>China, four hospitals in the west of China</p> <p>Case series</p> <p>URL:https://doi.org/10.1101/2020.03.12.20034686</p>	<p>Population setting: 34 infants admitted to hospital</p> <p>Patient demographics: 1-144 months (median 33 months); 14 (41.6%) male</p>	<p>Clinical history:</p> <ul style="list-style-type: none"> • Median incubation period 10.5 days (7.75-25.25 days) • Infections of other respiratory pathogens reported in 16 patients (47.06%) • Most common initial symptoms fever (76.47%), cough (58.82%), expectoration (20.59%), vomiting (11.76%), diarrhoea (11.76%) • Detailed lab results reported • Patchy lesions in lobules were detected by chest CT in 28 patients (82.36%) with typical adult symptom of ground-glass opacity was rare (2.94%) – late-onset pattern of lesions in lobules was noticed • Comorbidities were found in 6 patients (17.65%). <p>Clinical management: Multimodality therapies were employed, including antibiotic therapy (88.24%), antiviral therapy (82.35%), interferon-α nebulization (82.35%), corticosteroid therapy (14.71%), and oxygen inhalation supportive therapy (8.82%). The patients recovered from fever in 3.00 (2.00 - 4.00) days upon admission after treatments. The lesions in lobules still existed in discharge of patients, although great improvements were shown in CT scans after treatments.</p>

Author Country Study design URL	Population setting Patient demographics	Outcome results • Clinical history • Clinical management
<p>Wu et al.</p> <p>China</p> <p>Multicentre case series report from Chinese CDC</p> <p>URL:https://jamanetwork.com/journals/jama/article-abstract/2762130</p>	<p>Population setting: 965 paediatric cases in China</p> <p>Patient demographics: 549 cases aged 10-19 and 416 <10 years</p>	<p>Clinical history: N/A</p> <p>Clinical management: N/A</p> <p>549 cases aged 10-19 and 416 <10 years are both 1% of total cases in China (i.e. 2% of total Covid-19 cases)</p>
<p>Lu et al.</p> <p>China, Wuhan Children's hospital</p> <p>Case series</p> <p>URL:https://www.nejm.org/doi/full/10.1056/NEJMc2005073</p>	<p>Population setting: 171 children admitted to hospital</p> <p>Patient demographics: 1 day – 15 yrs; 18.1%<1yr; 23.4% 1-5yrs; 33.9% 6-10yrs; 24.6% 11-15yrs; 60.8% male; 39.2% female</p>	<p>Clinical history:</p> <ul style="list-style-type: none"> • Of the 31 <1 yrs, 0 were asymptomatic, 6 had URTI and 25 pneumonia; • Of the 40 1-5 yrs, 1 was asymptomatic, 12 had URTI and 27 pneumonia; • Of the 58 6-10 yrs, 14 were asymptomatic, 10 had URTI and 34 pneumonia; • Of the 42 11-15 yrs, 12 were asymptomatic, 5 had URTI and 25 pneumonia • Signs and symptoms were cough (48.5%), pharyngeal erythema (46.2%), fever (41.5%), diarrhoea (8.8%), fatigue (7.6%), rhinorrhoea (7.6%), vomiting (6.4%), nasal congestion (5.3%), tachypnoea on admission (28.7%), tachycardia on admission (42.1%) • Abnormalities on CT were ground-glass opacity (32.7%), local patchy shadowing (18.7%), bilateral patchy shadowing (12.3%), interstitial abnormalities (1.2%) • Detailed lab results reported. <p>Clinical management: Not reported</p>

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