Guidance for the clinical management of children admitted to hospital with suspected COVID-19

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This guidance is aimed at general paediatricians.

Separate guidance has been produced by the Paediatric Intensive Care Society on Covid-19 infection relevant to the paediatric critical care community: https://picsociety.uk/covid19/

1 Summary of the guidance:

Reassure parents and involve them in caring for their child, keep up-to-date using the evidence in Appendix 1 of this guidance, and communicate well with colleagues

Be extra-vigilant in children with pre-existing conditions but reassure parents that the risks of comorbidities is much greater in adults than children

Chest x-rays (CXR), bloods, and blood gases are not routinely indicated in all children. However, these should be monitored in children with persistent fever, altered fluid balance, signs of liver dysfunction, or respiratory failure

Although recommended in some adult papers, the following medical treatments are likely to have more side-effects than beneficial effects in children and are not routinely indicated: bronchodilators, systemic steroids, antibiotics, antivirals, and diuretics.

Despite emerging concern about Angiotensin Converting Enzyme (ACE) Inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs), there is insufficient evidence for stopping this if children have been taking them for pre-existing conditions and such an action may be harmful. In otherwise well children, paracetamol should be taken as the first-line antipyretic, and ibuprofen only taken with caution.

Escalate respiratory support as per local respiratory failure pathways. Do not use high flow nasal cannula oxygen if the child is saturating adequately with low flow oxygen.

It is crucial that we learn as much as we can about this emerging disease. Information should be reported to Public Health England. In all cases the Clinical Characteristics and Outcomes should be reported in the NIHR-funded Clinical Characterisation Protocol (CCP-UK) led by Professor Calum Semple (CCP@liv.ac.uk), and in the clinical database run by NHS England (currently under development).

2 Scope and background:

This guidance outlines key principles for the medical management of children admitted to hospital with COVID-19 (caused by SARS-CoV-2 virus). This guideline will evolve as we learn more about COVID-19 in children. The most up-to-date document will be hosted on the RCPCH website.

The guidance is based on literature review of published and unpublished data, expert opinion, and national/international guidelines. An up-to-date list of relevant papers is shown in Appendix 1. The internal validity of the observational studies (Appendix 1 Table 1) is generally low, and the results may not be directly generalisable to children in the UK, but these are useful for identifying themes. Interventional studies (in adults and children with COVID-19) will be listed in Appendix 1 Table 2. A summary protocol is shown in Appendix 5.

3 Key principles for good practice during this pandemic:

Reassure: Most children will have much milder illness than is seen in adults. Reassure children and parents, as they are likely to be concerned from information (and misinformation) in mainstream and social media. They might know an adult with the infection who may have been severely unwell, and it is important to explain differences between aults and children with COVID-19. In Italy, of 22512 people with COVID-19, there were 1625 deaths (none in people younger than 30 years) (1). In China, of 2134 children with COVID-19, only 1 died (0.05%) (2).

Involve parents: When parents feel disempowered they may become anxious and feel that their child is not being managed properly. The way healthcare professionals communicate with families is important (3). Reinforce that active monitoring and supportive therapy is the best strategy. Furthermore, identify ways to actively involve parents – in infection control procedures, entertaining and calming their child, supporting good nutritional intake, asking questions on their child's behalf, and helping avoid unnecessary investigations and interventions. Personal Protective Equipment (PPE) can look alarming to children, and it is important that parents and healthcare professionals proactively discuss the need for such measures, and reassure children. These crucial aspects of care are best done by parents.

Be vigilant: some children will develop complications and comorbidities. Although the medical literature suggests that the vast majority of children will have self-limiting illness without complications, be aware of local sepsis guidelines, acute kidney injury guidelines, and respiratory failure guidelines.

Teamwork: the whole multidisciplinary team must work together to ensure the best outcome for the child. During times of viral epidemic, parents and children want to see healthcare professionals adhere to the same guiding principles of practice. Deviation is undermining to other professionals, and parents and children will pick up on differences in practice (however subtle). Written and verbal communication between professionals is crucial to prevent this.

Minimising spread of the virus in hospital is crucial. Be aware of local and national recommendations for doing this.

Share data so that we can learn as the pandemic progresses. There is an ongoing NIHR research study (the Clinical Characterisation Protocol - https://isaric.tghn.org/UK-CCP/), an NHSE data sharing process for clinicians is under development and imminently ready to open), and a Public Health England reporting strategy. There is much sharing of unverified data on social media outlets. This can be useful and interesting but be aware this could also spread dangerous misinformation.

4 A summary of what we know about the pathology of COVID-19 infection (as of 19/03/2020 – this section will be updated as new evidence emerges)

COVID-19 is caused by a novel coronavirus (SARS-CoV-2). The first reported cases were in the Wuhan District of China, and appeared to be potentially from a zoonotic spillover at Huanan Seafood Wholesale Market. Subsequent cases were because of person to person transmission (4).

The virus is extremely contagious, particularly where there is close contact between people. The Reproduction number (R_0) estimates the number of people that an average person may infect if they carried the virus. This is currently estimated at around 3 (ie one person infects 3 people) (5). The virus is stable in aerosol form for hours and on solid surfaces for days (6).

The virus appears to directly infect cells via the ACE2 Receptor. This is expressed in various organs, including the lung. Cells in children's lungs express this receptor less than those in adult lungs. This may be one reason why the infection affects children less severely.

One proposed disease mechanism in severe cases is a 'cytokine storm' (7). This describes a cascade process whereby the virus leads to increased levels of cytokines that cause direct tissue damage, recruitment of neutrophils to tissues, and other pro-inflammatory effects. This damage can lead to Acute Respiratory Distress Syndrome. Various cytokines have been implicated in this process in severe and fatal cases (8–10). These include IP-10, MCP-1, TNF-1, IL1, and IL-6.

Extrapulmonary involvement and multi-organ failure have also been identified in people with severe or fatal illness. Some patients develop cardiac dysfunction (9). This may be due to viral-induced direct damage (cardiac tissue carries ACE receptors), or hypoxic damage in people with respiratory failure. One study found an increased risk of admission amongst children with a history of arrythmia (11). Viral infections can cause pericarditis, but this has not been consistently described in COVID-19. Liver damage and renal failure have been reported, and associated with severe infection (9).

5 Clinical and laboratory features in children – see Appendix 1 Table 1

No symptoms on admission consistently predict outcome in children, though in adults high fever on admission was associated with subsequent development of ARDS and death (12). The commonest features in the history of children with COVID-19 are fever and/or cough (each in around 50%). Fever in children with COVID-19 tends to subside within three days (13,14). The cough is typically dry (only one study looked at whether this is productive of sputum and reported this as 3% (14). Myalgia, lethargy, and gastrointestinal symptoms are also reported.

Although not reported in literature to date, parental smoking and use of electronic cigarettes (parents and older children), housing quality, and nutritional status may be associated with illness frequency and severity.

Leucopenia is a common finding (in around 30% of children). CRP is only raised in 10-20% of children. In one study that reported CRP levels in children (rather than just whether it was above a threshold) the maximum reported value was 33 (15). In one study, leucopenia and CRP>10 were associated with pneumonia (13).

6 Medical care (treatments and investigations)

6.1 Admission: Not all children with COVID-19 require admission. Many people with confirmed COVID-19 may be managed at home as per PHE guidance (https://www.gov.uk/government/publications/covid-19-stay-at-home-guidance/stay-at-home-guidance-for-people-with-confirmed-or-possible-coronavirus-covid-19-infection). We will evaluate UK data from admissions and provide a statement to clarify this in Version 3 of this guideline.

6.2 Radiology: In children, even those who are asymptomatic, chest x-rays and CT scans showed non-specific findings. They should only be done if there is a specific clinical question. They should not be conducted routinely, even if children require a small amount of oxygen on admission. It is crucial to isolate children and avoid movement around the hospital, so chest x-rays will be portable. It may be worth considering chest x-rays in children still requiring oxygen on Day 3 of admission, or those requiring CPAP. These would be unusual disease progressions and may signify severe illness, or early deterioration. Children not on HDU may require a chest x-ray if they have worsening hypoxaemia, particularly if they have pre-existing conditions.

Lobar collapse due to bacterial pneumonia is more likely if the child has respiratory failure, and persistent temperature. No studies have described lobar collapse, pneumothorax, or effusion in children with COVID-19. A number of studies advocate for the use of CT scans, but these will not help with diagnosis or management and are not indicated. Transferring infected children to the CT scanner puts other children at risk.

6.3 Fluids: Acute Kidney injury (AKI) is a complication of viral infections. Most children with mild illness do not require fluid restriction below normal maintenance values. If children have respiratory compromise consider fluid restriction as this may reduce the risk of ARDS. Be aware that febrile children, and those who are tachypnoeic, will have increased insensible losses. A small proportion of children may have pharyngitis, but this is not reported as a common problem with this virus so should not in most children affect oral intake. Monitor fluid balance, and measure daily weight in those children in whom fluid intake is a concern. Renal profile blood tests and urine dipstick are not required in all children but should be measured if there is a concern about fluid balance. Diuretics are not indicated routinely but should be considered (under consultant guidance) in some children with worsening respiratory failure requiring CPAP or NIV, particularly if there is evidence of pulmonary oedema on chest x-ray.

6.4 Antipyretics: Paracetamol is the first line antipyretic. Avoid ibuprofen in children with poor fluid intake or suspected AKI.

There are unsubstantiated reports of ibuprofen being implicated in severe cases of COVID-19 ((10)). Parents should be aware of potential theoretical risks of ibuprofen (one theory is that NSAIDs can upregulate expression of ACE receptors in the lung). If a child is requiring ibuprofen for relief of fever, be aware that this may in fact reflect significant inflammation, or be a sign of sepsis, and have a lower threshold for checking blood inflammatory markers.

6.5 Respiratory support: most children, even those with lung involvement, are unlikely to develop respiratory failure. It is important that children receive low flow nasal cannula (LFNC) oxygen if they are hypoxic, rather than high flow nasal cannulae (HFNC). If children are hypoxic despite LFNC, then HFNC can be tried (with full PPE). It should not routinely be used as a method of reducing work of breathing in children who are otherwise saturating adequately. There is no evidence in the literature about blood gases – these should not be done routinely. They can be used in children who despite administration of HFNC seem to require further respiratory support. In such children capillary blood gas (not venous) should be used to evaluate for pH and pCO2. Please note that ventilators may generate aerosols. Also remember that there is an anticipated shortage of ventilators in the UK, compared to the projected need, and these should only be used in children with documented respiratory failure after discussion with a consultant.

6.6 Antibiotics: For children with co-morbidities, such as cystic fibrosis, follow any disease specific guidance use antibiotics guided by cultures. There is no evidence around which antibiotic to use if bacterial pneumonia is suspected in children with COVID-19.

For children without pre-existing conditions consider antibiotics if

- They are unusually sick at admission/day 1
- They are not showing improvement by day 3 (particularly fever and/or still in oxygen)
- They have had bloods taken and CRP or WCC are raised. Ferritin may be useful as in adults this is associated with respiratory decline
- CXR changes should be mild in most children. If a CXR is done and there are obvious bilateral changes a macrolide might be a better first choice antibiotic as this may be associated with mycoplasma or atypical infection; if there are unilateral signs consider amoxicillin or co-amoxiclav. Bilateral CXR changes have been described in children that seem asymptomatic, so the findings should be tied with the clinical picture. These recommendations were part of the Alder Hey Children's Hospital and the Cheshire and Mersey Paediatric Network guidelines, and local guidelines may vary from this.
- If the cough is productive have a lower threshold for antibiotics
- A respiratory MC+S would be useful at the point of starting antibiotics
- It is important to note that sepsis and COVID-19 may share certain clinical features. If sepsis is considered, local guidelines for investigation and management should be followed.

There is limited evidence around how frequent bacterial coinfection is in children with COVID-19, or what the bacteria might be. One small (n=20) paediatric study found 20% of admitted children had mycoplasma but the authors do not specify how they found this, or whether they looked in everyone (11). A systematic review of studies looking at the rates of bacterial coinfection in the H1N1 pandemic (largely retrospective, again with varying levels of method reporting) estimated that 15% of patients had existing bacterial co-infection but this was lower in paediatric patients (the evidence base itself was poor and results were variable) (17). It is likely that bacterial co-infection is associated with morbidity (and in adults with mortality (18).

6.7 Antivirals: One high quality RCT compared lopinavir-ritonavir with usual care in 199 adults hospitalised with SARS-CoV-2 infection, and found no difference in the primary outcome (time to clinical improvement) or mortality (secondary outcome), but did report that length of stay, ICU duration, and risk of complications were lower (secondary outcomes) (19). No trials of antiviral medications have been conducted in children with COVID-19. The use of antivirals is not recommended in children. Emerging evidence will be listed in Appendix 1, Table 2.

6.8 Bronchodilators/treatment of children with asthma attacks: Wheeze is not a common problem in children with COVID-19. In people with lung involvement, this tends to be in the alveoli rather than the small airways. Bronchodilators should not be used routinely unless there is strong suspicion of bronchoconstriction (wheeze, and prolonged expiratory phase). The side effects of bronchodilators include pro-inflammatory effects on the alveoli, worsening of V/Q mismatch, and tachycardia. In children with asthma who are wheezy, use bronchodilation via MDI/spacer rather than nebulisation where possible as this reduces the risk of side effects, and minimises droplet spread. For children having an asthma attack treat them as they usually would be treated but avoid nebulisation. There is concern about the use of oral steroids causing viral shedding, but in the absence of evidence to suggest otherwise, these should be used as normal in children with asthma attacks.

6.9 Systemic steroids: Systemic steroids should not be used as a treatment for COVID-19. Some adult papers promote the use of steroids, and they were used in the outbreak in Wuhan. However they are likely to be harmful, immunosuppressive, and prolong viral shedding. They are unlikely to be beneficial. This is because there is no evidence of significant lung inflammation in children with COVID-19 so immunomodulation is not required. If children require ventilation and develop Acute Respiratory Distress Syndrome steroids may be useful (12) but there is no consistent and accurate way of identifying who will benefit. Anecdotal evidence from ICUs in Italy have suggested that early use of methylprednisolone in young adults may have benefit.

6.10 Liver dysfunction: There are reports of raised liver enzymes in children and adults with COVID-19. It is unclear how significant this is. Children with viral infections do get transient derangement of liver function, but this is self-limiting. It is more likely that this would happen in children who are generally unwell, those with pneumonia, and those receiving medical treatments that we will not be using. If taking bloods because the child appears unwell, check and record any derangement in liver function. If the derangement persists, check clotting. Do not check LFT routinely.

6.11 Hydroxychloroquine: Chloroquine and hydroxychloroquine may have antiviral activity. The mechanisms for this are unclear, but in vitro studies suggest it may modify virus-receptor binding (20,21). There are ongoing trials of chloroquine in patients with COVID_19 in China. Unverified sources suggest that the drug is superior to placebo with regards “inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course” (21). There is currently no evidence to date that hydroxychloroquine should be use in mild disease, nor that it will reduce severe illness or mortality. It is suggested that hydroxychloroquine will be a recommended drug in adults with COVID-19. In children it is unlikely to have clinically significant benefit when given routinely but may be considered in the rare event of PICU admission.

6.12 Discharge from hospital: NHS England has provided guidance on discharge that covers: discharge criteria; stay at home guidance; and discharge advice to patients. https://www.england.nhs.uk/coronavirus/secondary-care/discharge/.

APPENDIX 1 – SOURCES OF EVIDENCE

This is a repository of published and unpublished literature around COVID-9 or SARS-CoV-2 infection in children. Note in version 1 quality appraisal is not complete, but all evidence is low quality.

Web of Science
You searched for: **TOPIC:** (co-vid or covid or coronavirus or MERS-CoV) *AND* **TOPIC:** (clinic* or radiolog* or manage* or treat* or therapy*)
Refined by: PUBLICATION YEARS: (2020)
Timespan: All years. **Indexes:** SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC.

Handsearching (daily) of:

General medical journals

NEJM
BMJ
Lancet
PLoS Medicine
JAMA
BMC

Open access journals

BMJ Open
BMJ Open paediatrics
Plos One

Paediatric journals

ADC
JAMA Pediatrics
Lancet Child and Adolescent medicine
BMC Pediatrics

Respiratory journals

Lancet Res Med
Thorax
Chest
BMC respiratory medicine

https://ourworldindata.org/coronavirus

https://www.arcgis.com/apps/opsdashboard/index.html - /bda7594740fd40299423467b48e9ecf6

Table 1: epidemiological, demographic, and clinical characterisation observational studies relevant to COVID-19 in children (and selected adult studies – the adult studies will not be routinely added)

Study	Location	Patient population	Quality/ external generalisability	Summary findings
SELECTED ADULT STUDIES				
Xu (22) BMJ	Zheijang Province	62 Adults and children (n=2 children)	Retrospective, multi-centre Selection: all relevant patients, but this is a short time frame so not all cases included Ascertainment: adequate. Methods around identifying respiratory complications not well described Generalisability: mainly adults in China, early in the epidemic. Treated with regimen not used in UK	20/62 (32%) had pre-existing comorbidity 21/62 (34%) were associated with familial clusters Median duration of symptoms 4 days Commonest clinical features: fever (77%), cough (81%) myalgia/fatigue (52%) Respiratory: 2/62 (3%) developed shortness of breath 1/62 (1.6%) ventilated Bloods: FBC: 19/62 (31%) leucopenic Renal: not reported LFT: AST increased in 10/62 (16%)

Huang Lancet (9)	Wuhan	41 adults (no children were infected)	Retrospective multi centre Selection: all relevant patients, but this is a short time frame so not all cases included Ascertainment: adequate Generalisability: mainly adults in China, early in the epidemic. Treated with regimen not used in UK	13/41 (32%) had pre-existing comorbidity Median duration of symptoms 7 days Commonest clinical features: Fever (98%) Cough (76%) Myalgia/fatigue (44%) Respiratory: 22/41 (55%) developed dyspnoea (median at 8 days after onset) 13/41 (32%) required HFNC oxygen or more respiratory support 12/41 (29%) developed ARDS 4/41 (9%) required MV (2 of whom needed ECMO) Bloods: FBC: 10/41 (25%) leucopenic LFT: 15/41 (37%) raised AST AKI: 3/41 (7%)
Xu European Journal of Nuclear Medicine and Molecular Imaging (23)	Guangzhou	90 adults		45/90 (50%) had comorbidities Commonest clinical features: Fever (78%) Cough (63%) Fatigue/weakness (21%) Respiratory: not reported Bloods: FBC: 19/90 (21%) leucopenic LFT: not reported AKI: not reported Radiology: 69/90 showed abnormalities (see radiology section)
Chen Lancet (24)	Wuhan	99 Adults	Retrospective single centre Selection: all relevant patients, but this is a short time frame so not all cases included Ascertainment: adequate (?ARDS definition) Generalisability: mainly adults in China, early in the epidemic. Treated with regimen not used in UK	50/99 (51%) had pre-existing comorbidity Median duration of symptoms 7 days Commonest clinical features: Fever (83%) Cough (82%) Dyspnoea (31%) Respiratory: 81/99 (31%) developed dyspnoea 76% required oxygen 17% developed ARDS 4% required MV (3% needed ECMO) Bloods: FBC: 4% leucopenic (24% increased); 35% lymphopenic, 38% neutrophilic LFT: 35% raised AST AKI: 3%
PAEDIATRIC STUDIES				
Xia (11)	Wuhan	20 children	Retrospective single centre	Age: Median 2 years Sex: 13/20 (65%) male Comorbidities: 2/20 (10%) had previous cardiac surgery; 4/20 (20%) had known arrythmias; 1/20 (5%) had epilepsy Symptoms: Asymptomatic: 0 (0%) Fever: 12/20 (60%) Cough 13/20 (65%) Respiratory: 2/20 (10%) tachypnoeic Examination: Crackles 3/20 (15%), recession 1/20 (5%), cyanosis 1/20 (5%). Support required: not reported (suspect 0/20 required ICU) Bloods: FBC: 4/20 (20%) leucopenia; 2/20 (10%) leucocytosis LFT: 5/20 (25%) raised ALT AKI: not reported CRP: >3 in 7/20 (35%) Cardiac enzymes: CK-MB >25 in 5/20 (25%) Radiology: CXR not reported CT (20 children): Pulmonary - normal 4/20 (20%), Consolidation with halo sign 20/20 (50%) Ground glass 12/20 (60%) Nodules 3/20 (15%) Microbiology:

				Bacterial coinfection: 4/20 (20%) - mycoplasma
Chen (14)	Shenzen	31 children	Prospective single centre All received interferon, ribavirin, lpoanivir, ritonavir	Age: Median 6.8 years (range 1.5-17) Sex: 13.31 (42%) male Comorbidities: 2/31 (6.5%) – one asthma, one 'delicate kidneys' Symptoms: Asymptomatic 12/31 (38.7%) Fever: 14/31 (45%) duration median 2 days IQR 1-3 Cough: Respiratory: Not reported Bloods: FBC: 12/31 (38.7%) leucopenia; 17/31 (55%) lymphycytosis; 2/31 (6.5%) neutrophilic LFT: 2/31 (6.5%) Raised ALT AKI: 0/31 (0%) (creatinine) CRP: >8 in 4/3 (12.9%) Cardiac enzymes: not raised (though LDH abnormal in 39%) Radiology: Normal 19/20 (95%) CT showed ground glass changes, subpleural shadows and 'hazy pathces'
Tang (25)	Shenzen	26 children	Low quality evidence Retrospective single centre Selection: unclear if all cases included Ascertainment: definition of Covid19 as per national guidance Not yet peer-reviewed Methodology not clear	Age: mean 6.9 (0.7) years (1-13) Sex: 9/26 male (35%) Comorbidities: 0/26 (0%) Symptoms: Asymptomatic 9/26 (35%) Fever 11/26 (42%) Cough 12/26 (46%) Median duration before attendance at hospital unknown Respiratory: None (0%) developed ARDS or 'acute lung injury' Bloods: FBC: 50% leucopenia; 96% lymphocytosis LFT: 3/26 (12%) raised AST and/or ALT AKI: not reported CRP: >5 in 5/26 (19%) Myocardial enzymes: normal, except 6% had raised LDH Radiology (CXR/CT) Normal: 8/26 (31%) Unilateral changes: 11/26 (42%) Bilateral changes: 7/26 (27%)
Henry (26)	International	82 children	Low quality evidence Multicentre database No standardisation Ascertainment – unclear of case definition Not yet peer reviewed	Age: median 10 years (IQR 5-15). 27/82 (33%) adolescents Sex: 52.4% male Comorbidities: Symptoms (available in 25 children): 2/25 (8%) asymptomatic Fever 17/25 (68%) Cough 9/25 (36%) Median duration of symptoms: 3 days Respiratory: not reported Bloods: not reported Radiology: not reported
Cai (15)	Shanghai	10 children	Low quality evidence Single centre retrospective Not yet peer reviewed	Mean 6 years range 3 months – 11 years Sex: male:female 1:1.5 Comorbidities: Symptoms: 0/10 (0%) asymptomatic Fever 8/10 (80%) – resolved after 24 hours Cough 6/10 (60%) Median duration of symptoms: 2.5 days Respiratory: 0 children had dyspnoea, 0 required oxygen Bloods: FBC: 3/10 leucocytosis, 1/10 leucopenia, 1/10 neutrophilia CRP: >10 in 3/10 (max 33) LFT: ALT raised in 1/10 (100U/l) AKI: 0/10 Radiology:

				CXR: 4/10 (40%) bilateral patchy infiltrate, 6/10 normal Microbiology: Bacterial coinfection: not reported
Wang (27)	Shenzhen	34 children	Abstract only Low quality evidence Single centre retrospective review	Median age 8 years 1 months Sex: 14/34(42%) male Comorbidities: not reported Symptoms: Fever 17/34 (50%) Cough 13/34 (38%) Respiratory: "no severe cases were identified" Bloods: FBC: 1/10 leucopenia CRP: 'elevated' in 1 case LFT: not reported AKI: not reported Radiology: "bilateral multiple patchy or nodular ground-glass opacities and/or infiltrating shadows in middle and outer zone of the lung or under the pleura." Numbers nor rpeorted
Wang (28)	Northern China (6 provinces)	31 children	Abstract only Low quality evidence Retrospective multicentre review	Mean age 7 years Symptoms: Fever 20/31 (65%) Cough 14/31 (45%) Respiratory: Bloods: FBC: leucopenic in 2/31 (6%) CRP: 'elevated' in 3/30 (10%) LFT: 6/27 (22%) – unsure of which enzyme AKI: none Radiology: abnormal in 14 cases unsure how many had CT) – ground glass, patchy, nodules, subpleural, lower lobes
Wei (29)	China	9 infants <1 year	Letter Retrospective review Low quality	Median age 7 months Sex: 2/9 male Symptoms: Fever 4/9 URT symptoms 2/9 Asymptomatic: 1/9 Median duration of symptoms 1 day Respiratory: None required ICU or mechanical ventilation Family clustering in all infants
Liu (30)	Wuhan	6 children	Letter; 6 children (early in Wuhan outbreak) Low quality evidence Used treatments we are not recommending (antiviral, steroids, Ig)	Median age 3 years (range 1-7) Sex: 3/6 (50%) male Comorbidities: none Symptoms: Fever >39 in 6/6 Cough in 6/6 Respiratory: 1 required oxygen and also admission to ICU Bloods: FBC: leucopenia in 4/6, neutropenia 4/6 CRP: not reported LFT: not reported AKI: not reported LOS 5-13 days (median 7.5) Radiology: 4/6 had pneumonia on CT
Yu (31)	Wuhan	105 children	Low quality evidence; retrospective	Median age – not reported (1-15 years) Sex: 61/105 (59%) male Comorbidities; not reported Symptoms: not reported 8 cases were 'critically ill' (not clearly defined)
Dong (2)	China (CDC)	2143 children	Moderate-high quality evidence Multicentre, retrospective study across China	Median age 7 years (IQR 2-13) Sex: 1213/2143 (57%) male Comorbidities: not reported Symptoms: not reported

				Respiratory: severe (hypoxic) or critical (ARDS/ multi-organ failure) 5.9% (commonest in children <1 year) Mortality: 1 child died Laboratory and radiology findings – not reported
Lu (13)	Wuhan	171 children	Retrospective casenote review	Median age 6.7 years (1 day-15 years range) Sex: 104/171 male (61%) Symptoms: Fever in 41.5% (median duration 3 days (range 1-16) Max >39 in 9.4% Asymptomatic: 27/174 (more common in older children) Respiratory: 29% tachypnoeic on admission 2.3% required oxygen during admission Laboratory: 26% leucopenic Median CRP 4.0 12.3% increased ALT CRP>10 associated with pneumonia WCC <%.5 associated with pneumonia Radiology (CT) – 33% ground glass opacity; 12.3% bilateral patchy shadows; 1.2% interstitial.
Studies with adults and children, abut did not report paediatric data separately – listed but data not extracted				
Chang (32)				

Table 2 – Randomised controlled trials of interventions for COVID-19

Study ID	Study design	Location	Population	Intervention/ control arms	Outcomes	Results	Risk of bias
Cao (19)	RCT	China	199 hospitalised adults with proven COVID-19	Lopinavir-ritonavir vs usual care	Primary: Time to Improvement Secondary (selected): Mortality Length of ICU LOS (hospital) Complications	No difference between groups in time to improvement (primary outcome) No difference in 28 day mortality [19% (antiviral) vs 25% (usual care) difference -5.8% (-17.3 to +5.7)] LOS and ICU LOS shorter in antiviral group, and complications lower (see paper)	Selection: low risk Attrition: low risk Performance/detection: high risk Outcome reporting: low risk

Appendix 2: Descriptive summary of children who have died from COVID-19 related illness (as reported in the literature)

1) "As of March 8, 2020, there was one death. A 10-month-old child with in- tussusception had multiorgan failure and died 4 weeks after admission" [CHINA] (13)

Appendix 3: Summary data from UK confirmed admitted cases of COVID-19 (to be added as data collected)

Age
Gender

Comorbidities

Clinical outcome

Length of stay

Needed oxygen y/n; duration of oxygen

HFNC
CPAP/NIV
PICU for MV

Bronchodilators
Antibiotics
Chest x-rays

Appendix 4: Contributors, advisors, and reviewers

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Version 1 Ratified by Alder Hey CDEG 13th March 2020
Version 2 Ratified by BPRS March 18th 2020
Changes to Version 2: Pathology section added; antimicrobial section rewritten; hydroxychloroquine section added; Dong and Yu studies added;

Appendix 5 – brief protocol for the evidence summaries

As of Version 2:

Search as described in Appendix 1.

For observational studies: demographic and clinical data extracted around admission features and clinical progress. For RCTs, studies involving adults and/or children will be included. As more studies become available GRADE methodology will be utilised to make recommendations on treatment. Outcomes of interest include mortality, length of stay, ICU length of stay, comorbidities, duration of oxygen therapy, adverse effects of treatment (the COMET database will be searched to identify core outcome sets of relevance for Version 3). The Cochrane Risk of Bias Tool is used for study appraisal. Observational studies will be appraised using relevant tools (listed by each study).

References

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