Clinical characteristics, treatment outcomes of paediatric COVID-19: A systematic review and meta-analysis

Omar Irfan,1 Fiona Muttilab,1 Kun Tang,1,2 Li Jiang,1 Zohra S Lassi,3 Zulfiqar Bhutta 1,4

ABSTRACT
Objective Compare paediatric COVID-19 disease characteristics, management and outcomes according to World Bank country income level and disease severity.
Design Systematic review and meta-analysis.
Setting Between 1 December 2019 and 8 January 2021, 3350 articles were identified. Two reviewers conducted study screening, data abstraction and quality assessment independently and in duplicate. Observational studies describing laboratory-confirmed paediatric (0–19 years old) COVID-19 were considered for inclusion.
Main outcomes and measures The pooled proportions of clinical findings, treatment and outcomes were compared according to World Bank country income level and reported disease severity.
Results 129 studies were included from 31 countries comprising 10,251 children of which 57.4% were hospitalised. Mean age was 7.0 years (SD 3.6), and 27.1% had a comorbidity. Fever (63.3%) and cough (33.7%) were common. Of 3670 cases, 44.1% had radiographic abnormalities. The majority of cases recovered (88.9%); however, 96 hospitalised children died. Compared with high-income countries, in low-income and middle-income countries, a lower proportion of cases were admitted to intensive care units (ICUs) (9.9% vs. 36.0%) yet pooled proportion of deaths among hospitalised children was higher (relative risk 2.14, 95% CI 1.43 to 3.20). Children with severe disease received antimicrobials, inotropes and anti-inflammatory agents more frequently than those with non-severe disease. Subgroup analyses showed that a higher proportion of children with multisystem inflammatory syndrome (MIS-C) were admitted to ICUs (47.1% vs. 22.9%) and a higher proportion of hospitalised children with MIS-C died (4.8% vs. 3.6%) compared with the overall sample.
Conclusion Paediatric COVID-19 has a favourable prognosis. Further severe disease characterisation in children is needed globally.

INTRODUCTION
The coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus-2 has spread from a local outbreak in China to a global pandemic within months. On 31 December 2019, a cluster of cases with pneumonia of unknown cause emerged from Wuhan, China. On 30 January 2020, the WHO declared the coronavirus outbreak a Public Health Emergency of International Concern, and on 11 March 2020, a pandemic. As of 21 January 2021, there have been over 95.6 million confirmed COVID-19 cases and over 2.0 million associated deaths from 216 countries, areas or territories.1 Children under-19 years of age comprise a small proportion (1%-10%) of the total reported cases2-5 with a lower risk of developing critical illness from COVID-19 infection compared with adults.2 Prior systematic reviews of paediatric COVID-19 have described a mild disease in children with good outcomes.6-8 Since the publication of these reviews, the pandemic has spread extensively around the globe. In addition to pulmonary manifestations of COVID-19 in children, reports from Europe, North America, Latin America and Asia have emerged, describing a multisystem inflammatory syndrome children (MIS-C) related to COVID-19 infection.9-12 COVID-19 has also disrupted essential maternal and child health interventions, including outpatient visits and vaccinations for young children in most countries, further worsening the existing burden on healthcare provision and delivery.13

The objective of this review, in addition to providing a comprehensive update of the evolving paediatric COVID-19 literature, is a unique comparison of reported cases in low-income and middle-income countries (LMICs) to high-income countries (HICs) and of children with severe versus non-severe disease. Furthermore, the review provides a subgroup analysis of children presenting with symptoms of MIS-C and neonatal cases.

METHODS
The protocol of the review is registered with PROSPERO (CRD42020183134). This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).

SEARCH METHODS
were searched for preprints. No language restrictions were applied.

A search strategy was formulated and administered as shown in online supplemental table 1.

**STUDY SELECTION**

Observational studies reporting children (0–19 years old) with laboratory-confirmed COVID-19 (serology or RT-PCR) were considered for inclusion. Studies with a subset of children 0–19 years were included if disaggregated data for children were provided. Studies were screened for any overlap in paediatric cases by reviewing institution details and the period reported. Review articles, case reports, commentaries and letters not presenting any original data were excluded. Case reports were excluded to reduce risk of selection bias and over-representation of extreme cases. Covidence Software (2016) was used for screening by two reviewers independently and in duplicate. Key reference lists were screened for additional studies.

**DATA EXTRACTION**

Two reviewers conducted data extraction using a prepopulated data form. Data extracted included authors’ names, date of publication, study design, city, country, number of cases, gender, comorbidities, travel and contact history, diagnostic tests for COVID-19, clinical details, laboratory tests, radiological findings, management and outcomes. Disaggregated data by age groups (0–5 years, 5–10 years and >10 years old) and reported disease severity was extracted where available. Criteria for severe disease were as defined within each individual study and included admission to intensive care units (ICUs), use of mechanical ventilation, multiorgan failure and presence of hypoxia (oxygen saturation <92%).

**QUALITY ASSESSMENT**

Individual study quality was evaluated independently by the review authors using quality assessment tools developed by the National Heart Lung and Brain Institute (NHLBI)14 (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Study quality was scored out of 8, based on clarity of study objectives, case definition, consecutive inclusion of cases, comparability of included patients, definition and measurement of outcomes, length of follow-up, statistical methods and results. Studies with score 6–8 were considered to be good quality, 4–5 considered fair quality and <4 considered poor quality.

**DATA SYNTHESIS**

Categorical data were summarised as counts and proportions. The pooled proportions of reported findings were calculated using Comprehensive Meta-Analysis 2.2.027 using random-effects model. I² was calculated to examine statistical heterogeneity ($I^2>50\%$ considered high heterogeneity). The clinical features and outcomes were compared according to (1) World Bank country income level (HICs versus LMICs)13 and (2) reported disease severity (severe versus non-severe) using pooled proportions and their 95% CIs, supplemented by relative-risk (RR). Subgroup analyses of children with MIS-C and neonatal cases were conducted.

**RESULTS**

After removal of duplicates, 3350 citations were screened for inclusion. Full texts of 198 studies were screened and 129 studies were included (online supplemental figure 1). Sixty-nine studies were excluded as they either presented overlapping data, did not provide age-disaggregated data for children or were commentaries, editorials or reviews. In terms of study setting, 13 studies were population-based national surveillance studies, 94 studies included only children admitted to hospital and 22 studies reported patients presenting to outpatient clinics or emergency departments (hospitalisation rate of 24.2%, 385/1590).

Sixty studies were from HICs (n=6528) and 69 studies from LMICs (n=3723). Almost one-third of included studies were from China (36/129, 28.0%),15–21 24 25 26–33 35–37 39 42 43 52 53 55–57 71 74 79 81 82 85–87 93 98 109 110 113 120 133 136–138 one-fifth were from the USA (24/129, 18.6%)22–30 32 34 36–43 45 52 53 55–57 71 74 79 81 82 85–87 93 98 109 110 113 156 together comprising almost half of the included sample size (n=4758, 46.4%). The country of origin of included studies and study characteristics are summarised in online supplemental figure 2, tables 2 and 3.

**DEMOGRAPHICS AND EPIDEMIOLOGY**

A total of 9335 children from the 129 case series were included in the meta-analysis. Of 8455 children for whom initial disposition was reported, 4851 were hospitalised (57.4%). Among them, 55.5% were men. The patient’s ages ranged from 0 to 17 years with mean age of 7.0±3.6 years. Ninety-one of the 129 studies reported age-disaggregated data for infection incidence as shown in online supplemental table 4. Nearly half of the cases were >10 years of age. Contact exposure to COVID-19 was reported in 64.0% of cases. Travel history to an epicentre was reported in 13.0% cases. At least one underlying comorbidity was reported in 27.1% of cases. The most common reported comorbidities were immunosuppression (15.8%) and lung disease (12.5%).

**CLINICAL MANIFESTATIONS**

Table 1 summarises the clinical manifestations reported in the studies. There were 13.1% asymptomatic cases (95%CI 10.4% to 16.3%) who presented primarily through contact exposure in family-clusters (parents, siblings and other relatives). The most common presenting symptoms were fever (63.3%, 95%CI 58.6% to 68.4%) and cough (33.7%, 95%CI 29.6% to 38.1%) followed by nausea or vomiting (20.0%, 95%CI 16.5% to 24.0%) and diarrhoea (19.6%, 95%CI 16.1% to 23.7%). Other symptoms included dyspnoea, nasal-symptoms, rashes, kawasaki-like symptoms, conjunctivitis, fatigue, abdominal pain and neurological symptoms. Sixty-seven of the 129 studies reported age disaggregated data for clinical features (online supplemental table 5). Clinical features were similar in the three age groups: ≤5 years, >5 to ≤10 years, >10 years with higher prevalence of abdominal symptoms in children >5 years.

**RADIOLOGICAL AND LABORATORY FINDINGS**

One thousand five hundred and thirty cases out of 3670 (44.1%, 95%CI 39.5% to 48.9%) cases had radiological abnormalities: ground glass opacities (27.4%) were the most commonly reported abnormality.

Sixty-six studies provided details on laboratory-markers (table 2). Pooled analysis revealed increased C-Reactive Protein (CRP) (54.2%, 95%CI 41.5% to 66.3%), serum-ferritin (46.7%, 95%CI 32.3% to 61.7%), lactate dehydrogenase (LDH) (36.5%, 95%CI 26.5% to 47.8%) and d-dimers (35.2%, 95%CI 22.1% to 51.0%) as the most common abnormalities. Other reported abnormalities included elevated erythrocyte sedimentation rate (ESR), lymphopaenia, procalcitonin and biomarkers for organ
Table 1  Clinical symptoms among reported paediatric COVID-19 cases

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Events/total patients</th>
<th>Mean proportion % (95% CI)</th>
<th>Heterogeneity I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbidity</td>
<td>1590/6086</td>
<td>27.1 (23.1 to 31.5)</td>
<td>37.6</td>
</tr>
<tr>
<td>Fever</td>
<td>3576/6296</td>
<td>63.3 (58.6 to 68.4)</td>
<td>34.9</td>
</tr>
<tr>
<td>Cough</td>
<td>1807/5261</td>
<td>33.7 (29.6 to 38.1)</td>
<td>34.4</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>880/4243</td>
<td>20.0 (16.5 to 24.0)</td>
<td>25.7</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>796/4884</td>
<td>19.6 (16.1 to 23.7)</td>
<td>13.4</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>879/5332</td>
<td>17.5 (14.4 to 21.1)</td>
<td>23.7</td>
</tr>
<tr>
<td>Nasal symptoms</td>
<td>1080/5406</td>
<td>16.6 (13.9 to 19.7)</td>
<td>10.6</td>
</tr>
<tr>
<td>Rashes</td>
<td>744/4387</td>
<td>15.5 (11.9 to 19.9)</td>
<td>25.9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>709/4474</td>
<td>15.5 (12.6 to 19.3)</td>
<td>26.3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>626/4135</td>
<td>15.3 (11.9 to 19.4)</td>
<td>26.5</td>
</tr>
<tr>
<td>Kawasaki shock/sign</td>
<td>821/4365</td>
<td>13.3 (9.8 to 17.9)</td>
<td>30.6</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>1114/6084</td>
<td>13.1 (10.4 to 16.3)</td>
<td>15.4</td>
</tr>
<tr>
<td>Neurological symptoms</td>
<td>693/5475</td>
<td>12.1 (10.1 to 14.6)</td>
<td>17.6</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>529/4998</td>
<td>10.5 (7.8 to 14.0)</td>
<td>21.0</td>
</tr>
<tr>
<td>Pharyngeal erythema</td>
<td>428/3638</td>
<td>9.0 (6.7 to 12.0)</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Table 2  Laboratory and radiological features among reported paediatric COVID-19 cases

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Events/total patients</th>
<th>Mean proportion % (95% CI)</th>
<th>Heterogeneity I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory marker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP ↑</td>
<td>556/1165</td>
<td>54.2 (41.5 to 66.3)</td>
<td>21.4</td>
</tr>
<tr>
<td>Ferritin ↑</td>
<td>247/525</td>
<td>46.7 (32.3 to 61.7)</td>
<td>46.5</td>
</tr>
<tr>
<td>LDH ↑</td>
<td>356/922</td>
<td>36.5 (26.5 to 47.8)</td>
<td>35.6</td>
</tr>
<tr>
<td>Procalcitonin ↑</td>
<td>137/879</td>
<td>21.3 (12.2 to 34.5)</td>
<td>24.9</td>
</tr>
<tr>
<td>Leukocytes ↑</td>
<td>138/953</td>
<td>19.9 (13.3 to 28.8)</td>
<td>21.4</td>
</tr>
<tr>
<td>Lymphocytes ↓</td>
<td>359/1347</td>
<td>19.0 (12.8 to 27.1)</td>
<td>0.0</td>
</tr>
<tr>
<td>ESR ↑</td>
<td>248/838</td>
<td>18.9 (11.8 to 28.9)</td>
<td>0.0</td>
</tr>
<tr>
<td>IL-6 ↑</td>
<td>41/341</td>
<td>13.1 (5.5 to 28.2)</td>
<td>7.1</td>
</tr>
<tr>
<td>Leucopaenia (+)</td>
<td>77/1037</td>
<td>10.7 (7.7 to 14.6)</td>
<td>0.0</td>
</tr>
<tr>
<td>Lymphocytes ↑</td>
<td>66/1264</td>
<td>8.2 (4.9 to 13.5)</td>
<td>0.0</td>
</tr>
<tr>
<td>Neutrophils ↑</td>
<td>22/574</td>
<td>7.8 (4.8 to 12.4)</td>
<td>0.0</td>
</tr>
<tr>
<td>Biomarkers for organ injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>proBNP ↑</td>
<td>211/441</td>
<td>45.5 (28.5 to 63.5)</td>
<td>49.5</td>
</tr>
<tr>
<td>Troponin ↑</td>
<td>239/703</td>
<td>39.7 (24.7 to 57.0)</td>
<td>30.5</td>
</tr>
<tr>
<td>LFTs ↑</td>
<td>287/816</td>
<td>29.8 (20.3 to 41.6)</td>
<td>10.8</td>
</tr>
<tr>
<td>CKMB ↑</td>
<td>82/293</td>
<td>25.5 (13.4 to 43.0)</td>
<td>31.1</td>
</tr>
<tr>
<td>LFTs ↑</td>
<td>86/344</td>
<td>17.6 (7.6 to 35.6)</td>
<td>23.6</td>
</tr>
<tr>
<td>Coagulopathy markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-dimers ↑</td>
<td>272/711</td>
<td>35.2 (22.1 to 51.0)</td>
<td>19.1</td>
</tr>
<tr>
<td>Fibrinogen ↑</td>
<td>168/438</td>
<td>17.5 (7.6 to 35.4)</td>
<td>0.0</td>
</tr>
<tr>
<td>Radiological test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal CXR/C</td>
<td>1530/3670</td>
<td>44.1 (39.5 to 48.9)</td>
<td>35.0</td>
</tr>
</tbody>
</table>

injury including elevated levels of pro B-type natriuretic peptide, troponin and creatine kinase-MB as shown in table 2.

**MANAGEMENT**
Details of clinical management are as shown in table 3. Commonly used therapies among hospitalised children were antimicrobials (32.2%, 95% CI 25.2% to 40.1%), intravenous immunoglobulin (IVIG) (19.5%, 95% CI 13.5% to 27.2%) and systemic-steroids (19.3, 95% CI 14.9% to 24.9%). Other treatment regimens included aspirin, inotropic drugs, inhaled interferon-α (IFN-α), antimalarials and antivirals (ribavirin, oseltamivir, lopinavir, ritonavir and lomitavir). Mechanical ventilation was provided to 490 patients (12.2%, 95% CI 9.7% to 15.3%).

**PROGNOSIS AND SEVERE CASES**
One thousand three hundred and fifty-nine patients (22.9%, 95% CI 17.6% to 29.2%) were admitted to ICUs (table 3). Thirty-eight studies provided disaggregated data for severe cases (table 4). A higher proportion of children with severe disease had symptoms consistent with MIS-C and received antimicrobials, inotropes and anti-inflammatory agents compared with those with non-severe disease. There were no deaths among children.
Table 3 Clinical management and outcomes among reported paediatric COVID-19 cases

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Events/total patients</th>
<th>Mean proportion % (95% CI)</th>
<th>Heterogeneity I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical management</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>1345/3610</td>
<td>32.2 (25.2 to 40.1)</td>
<td>41.9</td>
</tr>
<tr>
<td>IVIG</td>
<td>698/3522</td>
<td>19.5 (13.5 to 27.2)</td>
<td>18.4</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>801/4229</td>
<td>19.3 (14.9 to 24.9)</td>
<td>23.7</td>
</tr>
<tr>
<td>Antiviral</td>
<td>527/4019</td>
<td>15.3 (11.1 to 20.7)</td>
<td>4.5</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>490/5406</td>
<td>12.2 (9.7 to 15.3)</td>
<td>15.5</td>
</tr>
<tr>
<td>Intotrops</td>
<td>354/3856</td>
<td>11.8 (8.3 to 16.4)</td>
<td>11.5</td>
</tr>
<tr>
<td>Antimalarial</td>
<td>336/3299</td>
<td>9.9 (6.9 to 14.0)</td>
<td>0.0</td>
</tr>
<tr>
<td>Aspirin</td>
<td>238/2588</td>
<td>9.0 (5.9 to 13.6)</td>
<td>78.1</td>
</tr>
<tr>
<td>Interferon</td>
<td>138/2598</td>
<td>7.7 (4.9 to 11.8)</td>
<td>0.0</td>
</tr>
<tr>
<td>Traditional medicine</td>
<td>22/4229</td>
<td>4.0 (2.8 to 5.6)</td>
<td>38.7</td>
</tr>
<tr>
<td><strong>Clinical outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovered</td>
<td>8704/9335</td>
<td>88.9 (86.0 to 91.2)</td>
<td>36.3</td>
</tr>
<tr>
<td>ICU admission</td>
<td>1359/9335</td>
<td>22.9 (17.6 to 29.2)</td>
<td>37.2</td>
</tr>
<tr>
<td>Deaths</td>
<td>96/6902</td>
<td>3.6 (2.8 to 4.5)</td>
<td>24.3</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; IVIG, intravenous immunoglobulin.

Table 4 Comparison of clinical symptoms, management and outcomes among reported paediatric COVID-19 non-severe (n=2402 cases, 64 studies) and severe (n=796 cases, 38 studies) cases

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-severe cases</th>
<th>Severe cases</th>
<th>RR severe vs non-severe (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/total patients</td>
<td>Mean proportion % (95% CI)</td>
<td>Events/total patients</td>
</tr>
<tr>
<td><strong>Clinical symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>1394/2404</td>
<td>51.4 (45.7 to 57.0)</td>
<td>608/756</td>
</tr>
<tr>
<td>Pharyngeal erythema</td>
<td>541/1149</td>
<td>8.6 (5.1 to 14.0)</td>
<td>411/835</td>
</tr>
<tr>
<td>Cough</td>
<td>587/1521</td>
<td>35.1 (29.2 to 41.5)</td>
<td>225/618</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>541/2283</td>
<td>19.8 (14.9 to 26.4)</td>
<td>351/764</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>206/1291</td>
<td>12.1 (8.7 to 16.6)</td>
<td>224/632</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>260/1646</td>
<td>12.7 (9.5 to 16.8)</td>
<td>237/701</td>
</tr>
<tr>
<td>Nasal symptoms</td>
<td>402/1659</td>
<td>14.1 (9.9 to 19.7)</td>
<td>91/652</td>
</tr>
<tr>
<td>Fatigue</td>
<td>193/1319</td>
<td>13.8 (10.4 to 18.0)</td>
<td>151/505</td>
</tr>
<tr>
<td>Kawasaki shock/sign</td>
<td>135/1243</td>
<td>8.5 (5.6 to 12.6)</td>
<td>242/695</td>
</tr>
<tr>
<td>Rash</td>
<td>168/1587</td>
<td>10.3 (7.6 to 13.7)</td>
<td>180/660</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>95/1193</td>
<td>8.1 (5.8 to 11.3)</td>
<td>184/621</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>144/1326</td>
<td>13.5 (10.6 to 17.1)</td>
<td>217/632</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>111/1621</td>
<td>7.5 (5.1 to 10.8)</td>
<td>116/657</td>
</tr>
<tr>
<td>Neurological symptoms</td>
<td>2002/2300</td>
<td>11.2 (9.0 to 13.4)</td>
<td>118/703</td>
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<td><strong>Clinical management</strong></td>
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<td>Mechanical ventilation</td>
<td>–</td>
<td>–</td>
<td>322/735</td>
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<tr>
<td>Mechanical ventilation</td>
<td>217/7115</td>
<td>26.5 (17.3 to 38.1)</td>
<td>136/567</td>
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<td>Antibiotics</td>
<td>127/805</td>
<td>20.2 (11.6 to 32.2)</td>
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<td>Antimicrobial</td>
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<td>12.6 (14.2 to 31.3)</td>
<td>365/566</td>
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<td>IVIG</td>
<td>73/717</td>
<td>10.1 (6.4 to 16.4)</td>
<td>123/537</td>
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<td>Systemic steroids</td>
<td>54/721</td>
<td>11.8 (7.2 to 18.8)</td>
<td>202/498</td>
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<td>Intotrops</td>
<td>46/721</td>
<td>8.9 (5.4 to 14.4)</td>
<td>265/575</td>
</tr>
<tr>
<td>Traditional medicine</td>
<td>18/723</td>
<td>7.4 (4.8 to 11.3)</td>
<td>171/498</td>
</tr>
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<td>Aspirin</td>
<td>11/883</td>
<td>6.7 (4.3 to 10.4)</td>
<td>4/57</td>
</tr>
<tr>
<td><strong>Clinical outcomes</strong></td>
<td></td>
<td></td>
<td>83/445</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; IVIG, intravenous immunoglobulin.
Global child health

where disaggregated data and outcomes, 60 studies were from HICs (n=6528) and 69 of the included studies that reported clinical characteristics were reported for 9335 children; 8704 cases (88.9%, 95% CI 86.0% to 91.2%) were definitively discharged, 96 died and remaining children either remained hospitalised at the time of reporting or were readmitted.

**COMPARISON OF OUTCOMES ACCORDING TO WORLD BANK COUNTRY CLASSIFICATION**

Of the included studies that reported clinical characteristics and outcomes, 60 studies were from HICs (n=6528) and 69 studies from LMICs (n=3723) as shown in table 5. Studies in LMICs included a higher proportion of hospitalised children (1981/3723, 53.2%) compared with HIC studies (2897/6528, 44.4%). Abdominal symptoms and symptoms consistent with MIS-C were more frequently reported in LMICs. A lower proportion of children in LMICs were admitted to the ICU (RR 0.56, 95% CI 0.50 to 0.63, p<0.05), mechanically ventilated (RR 0.32, 95% CI 0.26 to 0.39, p<0.05) and treated with different therapies; inotropes, antimicrobials, steroids, aspirin and IVIG. Only children in LMICs received inhaled IFN-α. Among the hospitalised cases, 40 deaths were reported in HICs compared with 56 in LMICs (pooled proportion 2.9% vs 5.2%). Risk-adjusted mortality according to severity of illness could not be calculated due to lack of data (table 5).

**SUBGROUP ANALYSES OF CHILDREN PRESENTING WITH MIS-C, AND COVID-19 IN NEONATES**

Thirty-one studies (n=1208) with 22 from HIC (n=602), reported series of children presenting with MIS-C. Fever, abdominal pain and diarrhoea were the most common symptoms. Nearly half of children (638/1208) who met criteria for MIS-C were admitted to ICU (449/638, 70.3% of which were from HIC) compared with 22.9% in the overall analysis (online supplemental tables 6 and 7).

---

**Table 5** Comparison of clinical symptoms, management and outcomes among reported paediatric COVID-19 cases in HICs (n=5641 cases, 60 studies) and LMICs (n=3694, 69 studies)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HICs Events/total patients</th>
<th>Mean proportion % (95% CI)</th>
<th>LMICs Events/total patients</th>
<th>Mean proportion % (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>2776/3332</td>
<td>72.0 (66.3 to 77.6)</td>
<td>1300/2964</td>
<td>50.0 (47.4 to 52.6)</td>
<td>0.64 (0.61 to 0.67)</td>
</tr>
<tr>
<td>Cough</td>
<td>955/2730</td>
<td>33.2 (27.5 to 39.5)</td>
<td>832/2531</td>
<td>39.2 (36.2 to 42.3)</td>
<td>0.82 (0.80 to 0.85)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>1669/3357</td>
<td>33.7 (27.4 to 38.5)</td>
<td>521/1729</td>
<td>20.8 (18.3 to 23.4)</td>
<td>0.60 (0.55 to 0.66)</td>
</tr>
<tr>
<td>Rash</td>
<td>491/2109</td>
<td>23.5 (17.9 to 33.5)</td>
<td>521/1729</td>
<td>20.8 (17.5 to 23.2)</td>
<td>0.46 (0.41 to 0.52)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>668/2374</td>
<td>30.3 (24.3 to 37.0)</td>
<td>212/1689</td>
<td>15.3 (12.6 to 18.3)</td>
<td>0.40 (0.35 to 0.46)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>309/2732</td>
<td>11.8 (8.4 to 15.4)</td>
<td>220/2296</td>
<td>9.5 (6.9 to 12.5)</td>
<td>0.45 (0.39 to 0.53)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>543/2454</td>
<td>21.3 (14.1 to 32.5)</td>
<td>336/2728</td>
<td>21.6 (18.1 to 25.2)</td>
<td>0.53 (0.47 to 0.60)</td>
</tr>
<tr>
<td>Kawasaki shock/sign</td>
<td>5831/2078</td>
<td>21.3 (14.1 to 32.5)</td>
<td>238/2278</td>
<td>21.4 (18.5 to 24.6)</td>
<td>0.57 (0.43 to 0.71)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>154/1943</td>
<td>8.1 (4.6 to 11.6)</td>
<td>315/2531</td>
<td>15.6 (13.3 to 18.3)</td>
<td>0.61 (0.54 to 0.70)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>457/2266</td>
<td>20.7 (16.4 to 25.0)</td>
<td>1691/869</td>
<td>16.6 (12.9 to 21.5)</td>
<td>0.45 (0.38 to 0.53)</td>
</tr>
<tr>
<td>Nasal symptoms</td>
<td>425/2549</td>
<td>17.4 (14.1 to 21.5)</td>
<td>269/2519</td>
<td>15.4 (13.2 to 17.8)</td>
<td>0.48 (0.41 to 0.56)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>527/2493</td>
<td>21.5 (15.7 to 28.4)</td>
<td>1251/1105</td>
<td>14.7 (12.4 to 17.3)</td>
<td>0.51 (0.44 to 0.57)</td>
</tr>
<tr>
<td>Neurological symptoms</td>
<td>493/3197</td>
<td>15.2 (11.5 to 19.0)</td>
<td>200/2278</td>
<td>10.5 (8.8 to 12.3)</td>
<td>0.57 (0.49 to 0.67)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>263/3248</td>
<td>3.1 (1.8 to 4.6)</td>
<td>851/1056</td>
<td>8.2 (5.9 to 10.6)</td>
<td>0.64 (0.51 to 0.77)</td>
</tr>
<tr>
<td>Pharyngeal erythema</td>
<td>73/1494</td>
<td>4.8 (3.0 to 6.1)</td>
<td>519/2531</td>
<td>40.7 (37.4 to 44.0)</td>
<td>4.20 (3.31 to 5.32)</td>
</tr>
</tbody>
</table>

HICs, high-income countries; ICU, intensive care unit; IVIG, intravenous immunoglobulin; LMICs, low-income and middle-income countries; RR, relative risk.
Disaggregated data were available on 184 neonates with fever; inability to feed/lethargy and dyspnoea were the most commonly reported symptoms. Twenty-one neonates (16.6%, 95% CI 11.2% to 23.9%) were asymptomatic at the time of diagnosis.

QUALITY ASSESSMENT OF INCLUDED STUDIES
One hundred and twenty-one studies were determined to be of good quality while eight were of fair quality (online supplemental table 8). Studies were primarily downgraded for incomplete case follow-up, missing data, and non-consecutive patient enrolment, with consecutive recruitment of patients, specific case definitions and inclusion criteria. The clinical presentation in children is heterogeneous, including a wide spectrum of clinical features. Fever and cough were the most commonly reported presenting symptoms, in line with the previously published systematic reviews. A U-shaped curve of severity has been demonstrated in children diagnosed with COVID-19 with infants under 1 year of age and adolescents 10–14 years of age at higher risk of developing severe COVID-19. Due to lack of age-disaggregated data, we could not reliably compare the frequency of severe cases by age group in this review. Reported risk factors for severe disease among children include age, viral load and presence of comorbidities. There is a possibility that children with comorbidities may have been hospitalised related to their underlying chronic condition and incidentally determined to have COVID-19 infection or investigated more extensively. Some of the common comorbidities reported in children with COVID-19 infection include asthma, immunosuppression, congenital heart disease, kidney disease and obesity.

Regional differences were identified in the comparison of clinical features, treatment and outcomes between HICs and LMICs. Pooled estimates of hospital mortality were higher in LMICs compared with HICs. Given that it was not possible to calculate risk-adjusted mortality rates for COVID-19, it is unclear whether observed differences in mortality are related to selection bias (eg, differences in severity of illness of included patients or differences in case definitions and inclusion criteria) or differences in available hospital resources. Nevertheless, there is ongoing concern that, in LMICs with high burden of illness and health system limitations, children with severe disease and MIS-C may be at greater risk for adverse outcomes and death than perceived to date. The differences in frequency of observed clinical features may be related to increasing recognition of MIS-C over the course of the pandemic and their inclusion in more recent COVID-19 case series, but is likely similar between HICs and LMICs.

Comparisons of clinical features and outcomes according to severity of illness were limited by heterogeneous reporting across the included case series. A higher proportion of children with severe disease demonstrated symptoms consistent with MIS-C (fever, abdominal symptoms, rash, neurological symptoms, conjunctivitis) and received IVIG, steroids and inotropes. Compared with previous reviews, several at an earlier stage of the pandemic, this review has several strengths. Using a broad search strategy implemented in English, Chinese and Spanish databases, we summarise evidence from 129 studies from 31 different countries, the largest sample-to-date. We excluded case reports to minimise selective reporting of extreme and atypical cases. We also attempted to reduce possible overlap in cases to prevent duplications. We identified differences in features from studies in HICs compared with LMICs, and between severe and non-severe cases, although with limited available data. Finally, we report subgroup analyses for neonates, and children presenting with MIS-C.

Regional differences in clinical characteristics and management have continued to evolve since the onset of the pandemic. Children have been noted to have relatively lower rates of severe illness and low mortality; however, they have been impacted by MIS-C, The findings of our review, the largest in terms of published systematic reviews on paediatric COVID-19, are consistent with previous reviews that identified predominance of infection in school-age children, slight male predominance, prevalence of comorbidities among children with COVID-19 and low hospitalisation and mortality rates. The clinical presentation in children is heterogeneous, including a wide spectrum of clinical features. Fever and cough were the most commonly reported presenting symptoms, in line with the previously published systematic reviews. A U-shaped curve of severity has been demonstrated in children diagnosed with COVID-19 with infants under 1 year of age and adolescents 10–14 years of age at higher risk of developing severe COVID-19. Due to lack of age-disaggregated data, we could not reliably compare the frequency of severe cases by age group in this review. Reported risk factors for severe disease among children include age, viral load and presence of comorbidities. There is a possibility that children with comorbidities may have been hospitalised related to their underlying chronic condition and incidentally determined to have COVID-19 infection or investigated more extensively. Some of the common comorbidities reported in children with COVID-19 infection include asthma, immunosuppression, congenital heart disease, kidney disease and obesity.

Regional differences were identified in the comparison of clinical features, treatment and outcomes between HICs and LMICs. Pooled estimates of hospital mortality were higher in LMICs compared with HICs. Given that it was not possible to calculate risk-adjusted mortality rates for COVID-19, it is unclear whether observed differences in mortality are related to selection bias (eg, differences in severity of illness of included patients or differences in case definitions and inclusion criteria) or differences in available hospital resources. Nevertheless, there is ongoing concern that, in LMICs with high burden of illness and health system limitations, children with severe disease and MIS-C may be at greater risk for adverse outcomes and death than perceived to date. The differences in frequency of observed clinical features may be related to increasing recognition of MIS-C over the course of the pandemic and their inclusion in
CONCLUSION

Our review suggests that children predominantly contracted mild form of infection but could be at risk of more severe outcomes. It is crucial to take into consideration risk factors including contact-exposure, underlying comorbidities, young age and male sex which may increase the risk of severe disease. While we have identified several elements that highlight the disease spectrum and higher risk of adverse outcomes in certain settings, such as LMICs, there is the need for much closer scrutiny of this illness globally with individual patient data analysis.

Contributors ZB conceptualised the study and secured funding, ZSL and OI drafted the study protocol, conducted the literature search, study screening, selection and data extraction and drafted the manuscript. LJ and KT designed the data collection instruments, collected data, carried out data analyses and reviewed and revised the manuscript. FM drafted the initial manuscript and reviewed and revised the data extraction and drafted the manuscript. LJ and KT designed the data collection patient data analysis.

Zulfiqar Bhutta http://www.unicef.org

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Clinical characteristics, treatment and outcomes of pediatric COVID-19: a systematic review and meta-analysis

Supplement file

Table 1: Search Strategy for MEDLINE

Table 2: Distribution of studies (N=129) according to Country of origin included in the review

Table 3: Characteristics of included studies (N=129)

Table 4: Age Distribution from 91 studies of disease prevalence

Table 5: Age Distribution from 67 case series of clinical features and outcomes

Table 6: Characteristics of included studies with MIS-C

Table 7: Characteristics of included studies from neonatal age group

Table 8: Quality assessment of included studies (N=129)

Figure 1: Flow diagram of the systematic review process

Figure 2: Global map of distribution of the studies included (N=129) in the review
Table 1: Search Strategy for MEDLINE

1- (coronavirus or "covid 2019" or "SARS2" or "SARS" or "SARS CoV19" or "severe acute respiratory syndrome coronavirus 2" or "coronavirus infection" or "severe acute respiratory pneumonia outbreak" or "novel cov" or 2019ncov or sars cov2 or cov2 or ncov or covid or covid19 or coronaviridae or "corona virus").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

2- "coronavirus infections".mp. or exp Coronavirus Infections/

3- exp Coronavirus 229E, Human/ or exp Coronavirus/ or exp Middle East Respiratory Syndrome Coronavirus/ or coronavirus.mp.

4- 1 or 2 or 3

5- (infant or neonate or newborn or child or children or pediatric* or paediatric or baby or babies or toddler).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

6- exp Infant, Low Birth Weight/ or exp Infant, Extremely Premature/ or exp Infant/ or exp Infant, Newborn/ or exp Infant, Premature/

7- 5 or 6

8- 4 and 7
Table 2: Distribution of studies (N=129) according to Country of origin included in the review

<table>
<thead>
<tr>
<th>Country</th>
<th>Count of reports</th>
<th>Sum of COVID-19 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>24</td>
<td>3443</td>
</tr>
<tr>
<td>China</td>
<td>36</td>
<td>1315</td>
</tr>
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<td>Canada</td>
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<tr>
<td>UK</td>
<td>9</td>
<td>867</td>
</tr>
<tr>
<td>Kazakhstan</td>
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<td>25 European Countries</td>
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</tr>
<tr>
<td>Italy</td>
<td>4</td>
<td>171</td>
</tr>
<tr>
<td>Spain</td>
<td>8</td>
<td>287</td>
</tr>
<tr>
<td>Korea</td>
<td>1</td>
<td>91</td>
</tr>
<tr>
<td>India</td>
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<td>145</td>
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<tr>
<td>Turkey</td>
<td>3</td>
<td>338</td>
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<tr>
<td>Jordan</td>
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<td>61</td>
</tr>
<tr>
<td>France</td>
<td>4</td>
<td>47</td>
</tr>
<tr>
<td>Iran</td>
<td>7</td>
<td>152</td>
</tr>
<tr>
<td>Brunei-Darussalam</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Chile</td>
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<td>27</td>
</tr>
<tr>
<td>Bangladesh</td>
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<tr>
<td>Brazil</td>
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<td>Kuwait</td>
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<tr>
<td>Peru</td>
<td>1</td>
<td>69</td>
</tr>
<tr>
<td>5 Latin American Countries (Mexico, Colombia, Peru, Costa Rica, Brazil)</td>
<td>1</td>
<td>409</td>
</tr>
</tbody>
</table>
Table 3: Characteristics of included studies (N=129)

<table>
<thead>
<tr>
<th>Study and year</th>
<th>Country</th>
<th>World Bank Country Classification</th>
<th>Total number (N)</th>
<th>Study setting</th>
<th>Mean age (years)</th>
<th>Males (N)</th>
<th>Past medical history and Contact history</th>
<th>Presenting signs and symptoms</th>
<th>Management (other than supportive care)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qiu, H 2020</td>
<td>China</td>
<td>LMIC</td>
<td>36</td>
<td>Patients presenting to hospital</td>
<td>8.3</td>
<td>23</td>
<td>Travel history (n=12) Contact history  (n=32) Comorbidities (NR)</td>
<td>Fever (n=13), cough (n=7), headache (n=3), nasal symptoms (n=2), GI symptoms (n=2)</td>
<td>Interferon (n=36), antivirals (n=14), oxygen (n=6)</td>
<td>Recovered (n=36) ICU admission (n=0)</td>
</tr>
<tr>
<td>Wang, D 2020</td>
<td>China</td>
<td>LMIC</td>
<td>31</td>
<td>Patients admitted in hospital</td>
<td>7.1</td>
<td>15</td>
<td>Travel history   (n=9) Contact history (n=1) Comorbidities  (n=0)</td>
<td>Asymptomatic (n=7), fever (n=20), cough (n=14), fatigue and diarrhea (n=3 each), sore throat (n=2), headache/dizziness (n=3), rhinorrhoea (n=2), vomiting (n=2)</td>
<td>Interferon (n=10), Antibiotics (n=6), antivirals (n=29), traditional medicine (n=9), IVIG (n=4)</td>
<td>Recovered (n=24) ICU admission (n=0)</td>
</tr>
<tr>
<td>Zheng, F 2020</td>
<td>China</td>
<td>LMIC</td>
<td>25</td>
<td>Patients admitted in hospital</td>
<td>3.0</td>
<td>14</td>
<td>Travel history   (n=9) Contact history (n=1) Comorbidities  (n=0)</td>
<td>Fever (n=13), cough (n=11), diarrhea (n=3), dyspnea (n=2), vomiting (n=2), abdominal pain (n=2), nasal congestion (n=2)</td>
<td>Interferon (n=2), Antibiotics (n=2), antivirals (n=2), steroids (n=2), IVIG (n=4), Mechanical ventilation (n=2)</td>
<td>Recovered (NR) ICU admission (n=2)</td>
</tr>
<tr>
<td>Author</td>
<td>Country</td>
<td>Region</td>
<td>Patients admitted in hospital</td>
<td>Patients presenting to hospital</td>
<td>Travel history (n=20)</td>
<td>Contact history (n=13)</td>
<td>Comorbidities (NR)</td>
<td>Symptomatics</td>
<td>Antibiotics</td>
<td>Interferon</td>
</tr>
<tr>
<td>----------</td>
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<td>Xia, W.</td>
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<td>LMIC</td>
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<td></td>
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<td>Contact history (n=13)</td>
<td>Comorbidities (NR)</td>
<td>Cough (n=13), fever (n=12), diarrhea (n=3), dyspnea (n=2), sore throat (n=1), fatigue (n=1)</td>
<td>NR</td>
<td>Recovered (n=19)</td>
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<tr>
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<td>15</td>
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<td>Travel history (n=3)</td>
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<td>Comorbidities (NR)</td>
<td>Asymptomatic (n=8), fever (n=5), cough or nasal congestion (n=1)</td>
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<td>Recovered (n=5)</td>
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<tr>
<td>Cai, J.</td>
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<td>NR</td>
<td>Recovered (n=10)</td>
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<tr>
<td>Wei, M</td>
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<td>9</td>
<td>Patients admitted in hospital</td>
<td>Travel history (n=8)</td>
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<td>Comorbidities (NR)</td>
<td>Asymptomatic (n=6), fever or cough (n=3)</td>
<td>Interferon given to all patients; antivirals (n=2)</td>
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<td>Su, L.</td>
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<td>Contact history (n=9)</td>
<td>Comorbidities (n=0)</td>
<td>Asymptomatic (n=5), fever (n=4), cough (n=2), rhinorrhea (n=1)</td>
<td>Interferon (n=9) antivirals (n=6), mechanical ventilation (n=9)</td>
<td>Recovered (NR)</td>
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<td>Zhou, Y.</td>
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<td>LMIC</td>
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<td>Travel history (n=8)</td>
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<td>Fever or cough (n=6 each), sputum production (n=4), mechanical ventilation (n=2), antibiotics (n=5),</td>
<td>Recovered (n=5)</td>
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<td>Recovered (n=5)</td>
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<tr>
<td>Authors</td>
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<td>Contact history (n=5)</td>
<td>Comorbidities (n=3)</td>
<td>nausea/ vomiting (n=4), diarrhea (n=3), fatigue (n=1) or headache (n=1), sore throat or nasal symptoms (n=8)</td>
<td>Antivirals (n=6), systemic steroids (n=4), IVIG (n=4)</td>
<td>ICU admission (n=8)</td>
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<td>---------</td>
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**Comorbidities:**
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- Fever (n=23), cough (n=0), fatigue (n=8), dyspnea (n=10), diarrhea (n=13), nausea or vomiting (n=0), abdominal pain (n=15), sore throat or nasal symptoms (n=0), neurological (n=5), kawasaki signs (n=16), rashes (n=20), conjunctivitis (n=15)
- Fever (n=23), cough (n=0), fatigue (n=8), dyspnea (n=10), diarrhea (n=13), nausea or vomiting (n=0), abdominal pain (n=15), sore throat or nasal symptoms (n=0), neurological (n=5), kawasaki signs (n=16), rashes (n=20), conjunctivitis (n=15)
- Fever (n=23), cough (n=0), fatigue (n=8), dyspnea (n=10), diarrhea (n=13), nausea or vomiting (n=0), abdominal pain (n=15), sore throat or nasal symptoms (n=0), neurological (n=5), kawasaki signs (n=16), rashes (n=20), conjunctivitis (n=15)

**Interventions:**
- Mechanical ventilation (n=6), IVIG (n=23), systemic steroids (n=15) inotropes (n=9), aspirin (n=17)
- Mechanical ventilation (n=6), IVIG (n=23), systemic steroids (n=15) inotropes (n=9), aspirin (n=17)
- Mechanical ventilation (n=6), IVIG (n=23), systemic steroids (n=15) inotropes (n=9), aspirin (n=17)
- Mechanical ventilation (n=6), IVIG (n=23), systemic steroids (n=15) inotropes (n=9), aspirin (n=17)

**Outcome:**
- Recovered (n=15)
- Recovered (n=149)
- Recovered (n=34)
- Recovered (n=37)
- Death (n=0)
- Death (n=1)
- Death (n=0)
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<td>Bayeshev, D 2020</td>
<td>Kazakhstan</td>
<td>650</td>
<td>Data was reported from the official medical electronic database of the Country</td>
<td>Travel history: (NR)</td>
<td>Fever: (n=59), cough: (n=96), fatigue: (n=7), dyspnea: (n=12), diarrhea: (n=13), asymptomatic: (n=315), sore throat or nasal symptoms: (n=119), rashes: (n=1)</td>
<td>Mechanical ventilation: (n=3)</td>
<td>Recovered: (n=650)</td>
<td>ICU admission: (n=6)</td>
<td>Death: (n=0)</td>
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<td>Travel history: (NR)</td>
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<td>Recovered: (n=50)</td>
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### Table 1: Characteristics of Patients Presenting to Tertiary Care Centres

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<th>Country</th>
<th>Region</th>
<th>Code</th>
<th>Patients Presenting to Tertiary Care Centre Outpatient Department</th>
<th>Contact History (NR)</th>
<th>Comorbidities (N)</th>
<th>Mechanical Ventilation</th>
<th>ICU Admission</th>
<th>Death</th>
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<tr>
<td>Bhavsar, M 2020</td>
<td>USA</td>
<td>HIC</td>
<td>81</td>
<td>Patients admitted in 12 hospitals in the city</td>
<td>Travel History (NP)</td>
<td>Fever (n=63), cough (n=38), diarrhea (n=26), nausea or vomiting (n=26), abdominal pain (n=26), neurological symptoms (n=7), rashes (n=8), conjunctivitis (n=7)</td>
<td>Mechanical ventilation (n=3), antivirals (n=6), IVIG (n=1), systemic steroids (n=15), antimalarials (n=10), inotropes (n=9), aspirin (n=1)</td>
<td>ICU admission (n=28)</td>
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<tr>
<td>Montoya, J 2020</td>
<td>Peru</td>
<td>LMIC</td>
<td>69</td>
<td>Cancer patients admitted to tertiary care centres</td>
<td>Travel History (NP)</td>
<td>Fever (n=12), cough (n=12), dyspnea (n=11), diarrhea (n=3), nausea or vomiting (n=3), abdominal pain (n=2), sore throat or nasal symptoms (n=11), rashes (n=1), asymptomatic (n=37)</td>
<td>Antibiotics (n=9), interferon (n=9), systemic steroids (n=9)</td>
<td>ICU admission (n=3)</td>
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**NR** = Not reported

LMIC: Low and middle-income Country, HIC: High-income Country
Table 4: Age Distribution from 91 studies of disease prevalence

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<th>Age</th>
<th>Frequency (%)</th>
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<td>0 to ≤5 years</td>
<td>3149 (36.9)</td>
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<td>&gt;5 to ≤10 years</td>
<td>1668 (19.6)</td>
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<tr>
<td>&gt;10 years</td>
<td>3712 (43.5)</td>
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<tr>
<td>Total</td>
<td>8529</td>
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<td>Age bands</td>
<td>Fever</td>
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<tr>
<td>0 to ≤5 years</td>
<td>99/181 (54.7)</td>
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<tr>
<td>&gt;5 to ≤10 years</td>
<td>87/133 (65.4)</td>
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<tr>
<td>&gt;10 years</td>
<td>60/132 (45.4)</td>
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<tr>
<td>Clinical features</td>
<td>Frequency (%)</td>
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<tr>
<td>Recovered</td>
<td>176/196 (90.3)</td>
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<tr>
<td>Severe/ICU admission</td>
<td>188/1708 (11.0)</td>
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<tr>
<td>Not yet discharged</td>
<td>19/196 (9.7)</td>
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<tr>
<td>Deaths</td>
<td>1/1360 (0.07)</td>
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Table 6: Clinical symptoms among MISC from 31 studies

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<td>264/1182</td>
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<td>Fever</td>
<td>1008/1208</td>
<td>94.2 (88.7-97.1)</td>
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<td>Kawasaki shock/sign</td>
<td>708/1208</td>
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<td>Abdominal pain</td>
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<td>58.1 (49.6-66.1)</td>
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<td>Diarrhea</td>
<td>308/563</td>
<td>54.0 (45.9-61.9)</td>
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<td>Conjunctivitis</td>
<td>461/1163</td>
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<td>Nausea/vomiting</td>
<td>280/563</td>
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<td>220/1181</td>
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<td>Neurological symptoms</td>
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<td>Fatigue</td>
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<td>16.3 (9.6-26.3)</td>
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<td>94/766</td>
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<td>Nasal symptoms</td>
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<td>Pharyngeal erythema</td>
<td>298/1099</td>
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Clinical management

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<td>IVIG</td>
<td>618/1207</td>
<td>69.1 (55.1-80.4)</td>
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<td>Inotropes</td>
<td>255/934</td>
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<td>Antibiotics</td>
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<td>Aspirin</td>
<td>201/951</td>
<td>31.7 (19.5-47.1)</td>
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<td>Systemic steroids</td>
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<td>Mechanical ventilation</td>
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Clinical outcomes

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<td>Deaths</td>
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<td>4.8 (3.6-6.3)</td>
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<tr>
<td>Characteristics</td>
<td>Events/total patients</td>
<td>Mean proportion % (95% CI)</td>
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<td>Fever</td>
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Supplemental material

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Figure 1: Flow diagram of the systematic review process

Records identified through database searching (n = 3350)

Additional records identified through other sources (n = 33)

Records after duplicates removed (n = 2428)

Records screened (n = 2428)

Records excluded (n = 2230)

Full-text articles assessed for eligibility (n = 198)

Full-text articles excluded, with reasons (n = 69)

Studies included in quantitative synthesis (n = 129)

Population-based national surveillance studies (n = 13)

Hospital in-patient ward or intensive care based studies (n = 94)

Out-patient clinics or emergency departments based studies (n = 22)
Figure 2: Global map of distribution of the studies included (N=129) in the review