

## Steckbrief COVID-19 – Clinical characteristics in children and adolescents

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<http://www.kinderkliniken.insel.ch/de/coronavirus/>

<b>Causative agent</b>	SARS-CoV-2 <sup>1</sup>
<b>Receptor</b>	<ul style="list-style-type: none"> <li>• Angiotensin-Converting Enzyme 2 (ACE2 receptor)<sup>2</sup></li> <li>• ACE2 mainly expressed in lung, intestinal, renal and vascular tissues<sup>3</sup>, but also in oral mucosa [Xu]</li> </ul>
<b>Immunology/ Pathogenesis</b>	<ul style="list-style-type: none"> <li>• severe disease in adults associated with early functional exhaustion of innate immunity (NK cells) and CD8+ cytotoxic T cell activity<sup>4</sup>, innate immune suppression not supported by other authors [Kox]</li> <li>• severe disease associated with cytokine storm similar to MAS/secondary HLH<sup>5</sup></li> <li>• convalescent sera contain neutralizing antibodies against the S1/S2 spike protein; titers correlate positively with age (adults) [Wu]</li> <li>• protective role of reduced cellular expression or higher circulating ACE2 levels in children<sup>6</sup> and of “trained innate immunity”?<sup>7</sup></li> </ul>
<b>Transmission</b>	<ul style="list-style-type: none"> <li>• droplet; contact  <math>\frac{1}{2}</math> life in aerosol ~1 hour, <math>\frac{1}{2}</math> life on plastic/steel 6-8 hours<sup>8,9</sup>; detected also in patient rooms [Chia], clinical significance unknown</li> <li>• viral transmission can start 1-2 days before the onset of symptoms («serial interval» &lt; incubation period<sup>10,11</sup>; recovery of virus from NPA before onset of symptoms (Woelfel R)<sup>12</sup></li> <li>• viral RNA in NPA from children until <u>6 to &gt;22</u> days after disease onset<sup>13-16</sup></li> <li>• viral RNA in feces from day <u>-5 to &gt; 4 weeks</u> after disease onset<sup>14,16-20</sup></li> <li>• viral load and duration of shedding do not correlate with severity of COVID-19<sup>15,16,21</sup></li> <li>• <u>vertical transmission: no RT-PCR positive cases reported</u>; 2 reports on the presence of IgM in neonates to be interpreted with caution<sup>22,23</sup></li> <li>• currently no evidence of transmission in human milk [Lackey]</li> </ul>
<b>Incubation period</b>	4-6 days (range, 1 to >14 days)
<b>Epidemiology</b>	<ul style="list-style-type: none"> <li>• basic reproduction rate <math>R_0</math> 2.2 (90% CI, 1.4-3.8)<sup>24,25</sup></li> <li>• high risk for «superspreader events» (dispersion parameter <math>k \downarrow</math>)<sup>25</sup></li> <li>• <u>Switzerland</u>: age &lt;10 years, 0.4%; age 10-19 years, 2.6% of all cases</li> <li>• <u>Sweden</u>: age &lt;10 years, 0.5%; age 10-19 years 1.3% of all cases</li> <li>• <u>Germany</u>: survey on hospitalized children infected with SARS-CoV-2</li> <li>• <u>Spain</u>: 0.8% of COVID-19 positive persons were &lt;18 years of age<sup>26</sup></li> <li>• transmission to children mainly within families<sup>14,15,18,26-28</sup></li> <li>• modelling suggests that <u>subclinical</u> infection (NOT resistance to infection) is the major factor explaining low case numbers in children (Davies)</li> <li>• children unlikely to be sources case in household transmission (Zhu)</li> <li>• population screening data from Iceland with no infections among &lt;10-year-old vs. 0.8% in older individuals<sup>29</sup></li> </ul>

<p><b>Clinical manifestations</b></p>	<ul style="list-style-type: none"> <li>• common: asymptomatic<sup>19,30,31</sup></li> <li>• common: fever <u>~40%</u><sup>14,15,27,28,30,32-35</sup>; 56% in <u>US series</u> (163/291 patients)</li> <li>• common: cough <u>~50%</u><sup>14,15,28,30,34,35</sup></li> <li>• common: pharyngitis <u>~40%</u><sup>28</sup></li> <li>• common: mild diarrhea<sup>14,18,31,32</sup></li> <li>• <u>infrequent</u>: rhinorrhea<sup>28,35</sup>, <u>wheezing</u><sup>14,15,27,31,32,34</sup></li> <li>• <u>infrequent</u>: malaise, headache, myalgias</li> <li>• olfactory dysfunction very common in adults [<u>Menni</u>], not reported in children</li> <li>• conjunctivitis (RT-PCR positive) reported in adults<sup>36</sup></li> <li>• <b>covid toe</b>: painful, vasculitic, frost-bite like finger/toe lesions in often otherwise asymptomatic children reported (Spain, US)</li> <li>• <b>varicella-like papulovesicular rash</b> reported in adults and children in Italy<sup>37,38</sup></li> <li>• <b>acute systemic inflammatory syndrome</b> resembling toxic shock syndrome/Kawasaki disease reported in several countries (<u>UK</u>, Spain, Switzerland, Italy, US); RT-PCR in NPA typically negative; serology positive</li> <li>• co-infections reported (e.g. Influenza A/B, <i>M. pneumoniae</i>)<sup>26,30,35</sup></li> </ul>
<p><b>Laboratory findings</b></p>	<p><u>CBC differential, CRP, chemistry generally uncharacteristic</u><sup>19,28,35,39</sup></p> <ul style="list-style-type: none"> <li>• <u>Children</u>: leucopenia, lymphopenia and thrombocytopenia uncommon<sup>14,15,39</sup>; CRP/PCT normal to moderately elevated<sup>14,28,30,34,35,40</sup></li> <li>• <u>Adults with severe lung disease</u>: lymphopenia (NK, CD8), IL-6↑, CRP&gt;200, PCT&gt;0.5, ferritin&gt;2500 D-Dimers&gt;2500, LDH↑<sup>4,41</sup> [<u>Petrilli</u>]</li> </ul>
<p><b>Diagnosis</b></p>	<ul style="list-style-type: none"> <li>• RT-PCR from NPA; some laboratories offer quantitative copy number</li> <li>• seroconversion ~1 week after onset of symptoms (<u>Woelfel R</u>)</li> <li>• Nasal swab RT-PCR less sensitive than BAL/sputum in severely ill adults<sup>42</sup></li> <li>• IgM/IgA appear on day ~5 of illness, IgG on day ~14 (adults)<sup>43</sup></li> <li>• commercial IgM/IgG tests are available on the market, currently evaluated</li> </ul>
<p><b>Radiology</b></p>	<ul style="list-style-type: none"> <li>• conventional CXR: normal or non-specific findings</li> <li>• chest CT: unilateral or bilateral, uni- or multifocal, peripheral, commonly subpleural lesions; focal lesions typically with central consolidation and halo sign or ground glass opacities (GGOs)<sup>15,28,30,34,35,44</sup></li> <li>• <u>no</u> pleural effusion<sup>30,44</sup></li> <li>• <u>no</u> hilar lymphadenopathy<sup>30,44</sup></li> </ul>

<b>Clinical course</b>	<ul style="list-style-type: none"> <li>• common: asymptomatic (reported all ages)<sup>13-15,27</sup></li> <li>• common: upper respiratory tract infection (children and healthy adults)<sup>14,28</sup></li> <li>• common: pneumonia (absent, mild or moderate clinical disease)<sup>28,30,34,45,46</sup></li> <li>• very rare: severe lung disease requiring mechanical ventilation (3/171 [1.8%] reported by Lu<sup>28</sup>, 2 infants reported in detail<sup>35</sup>)<sup>18,28,34</sup></li> <li>• several fatal cases in SARS-CoV-2 positive infants and children reported<sup>28,47</sup>; no details on causes of death available</li> <li>• first pediatric fatal case in <a href="#">Germany</a> reported 09/04/2020</li> <li>• hospitalization, ICU admission and death more common in &lt;1-year old in <a href="#">China</a><sup>31</sup>, <a href="#">Spain</a><sup>26</sup>, <a href="#">US</a>, <a href="#">Germany</a></li> </ul>
<b>Clinical course - immunodeficiency</b>	<ul style="list-style-type: none"> <li>• <b>Primary immunodeficiency (PID):</b> severe disease appears to be rare, no deaths among patients with PID reported to <a href="#">IPOP1</a></li> <li>• <b>Cancer:</b> several cases of pediatric cancer patients in Italy, Spain, Switzerland, China; outcome pending, no deaths reported</li> <li>• <b>Transplant patients:</b> No evidence for severe disease among solid organ transplant recipients in Italy<sup>48</sup></li> <li>• <b>Autoimmune disease:</b> Benign course in 8 children with IBD on immunomodulators/biologicals reported<sup>46</sup></li> </ul>
<b>Clinical course - pregnancy</b>	<ul style="list-style-type: none"> <li>• infections reported mainly in 3rd trimester; characteristic complications have not been reported to date<sup>49,50</sup></li> <li>• no virologically confirmed evidence for vertical transmission and fetal infection<sup>50-53</sup>; 2 reports on IgM positive neonates to be interpreted with caution<sup>22,23</sup></li> </ul>
<b>Clinical course - neonates</b>	<ul style="list-style-type: none"> <li>• asymptomatic infection in neonates (including normal chest CT) has been reported<sup>18,30,51</sup></li> <li>• 3 infected neonates reported with early and short viral RNA shedding (DOL #2+4 only)<sup>54</sup></li> <li>• complicated perinatal/postnatal courses among <u>non-infected neonates</u> of COVID-19 infected mothers have been reported<sup>55</sup></li> </ul>
<b>Treatment</b>	<ul style="list-style-type: none"> <li>• supportive</li> <li>• currently no evidence from clinical trials available</li> <li>• drugs with antiviral activity against SARS-CoV-2 in vitro: remdesivir (nucleoside analog)<sup>56,57</sup>, lopinavir/ritonavir<sup>57</sup>, hydroxychloroquine<sup>58</sup></li> <li>• Compassionate use program <u>without control group</u> reported 68% respiratory improvement rate using remdesivir in severe disease<sup>59</sup></li> <li>• Lopinavir/ritonavir reported <u>ineffective</u> in one controlled trial<sup>60</sup></li> <li>• immunomodulation with mAbs, e.g. tocilizumab, siltuximab (anti-IL6) currently investigated</li> <li>• ACE2/viral entry blocker (e.g., Nafamostat) effective in vitro<sup>61,62</sup></li> <li>• <u>recommendations against use of NSAID are NOT supported by the <a href="#">EMA</a>, <a href="#">WHO</a>, expert opinion<sup>63</sup></u></li> </ul>

<b>Prevention</b>	<ul style="list-style-type: none"><li>• Inpatients: precautions according to <a href="#">Swissnoso/PIGS</a></li><li>• Outpatients: precautions according to <a href="#">BAG</a>, <a href="#">KAZA</a></li><li>• Neonates: no separation of well mother/child pairs needed (<a href="#">Swissnoso/PIGS</a>, <a href="#">SGGG</a>, <a href="#">WHO</a>, <a href="#">DGPI</a>, <a href="#">AAP</a>); management IMC/NICU according to local infection control policy</li><li>• BCG vaccine: nonspecific protective effect currently controversial [<a href="#">Szigeti</a>]</li><li>• <u>Italian hospitals report &gt;80% reduction in pediatric ER visits an increase in deaths unrelated to COVID-19</u> [<a href="#">Lazzerini</a>]</li><li>• <u>Summary of vaccine pipeline with 5 products in phase I studies</u> [<a href="#">Le</a>]</li></ul>
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