

Steckbrief COVID-19 – Clinical characteristics in children and adolescents

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Causative agent	SARS-CoV-2 ¹ (betacoronavirus, most closely related to SARS-CoV among the 7 human coronaviruses)
Receptor	<ul style="list-style-type: none"> • Angiotensin-Converting Enzyme 2 (ACE2 receptor)² • ACE2 expressed in upper/lower respiratory tract, oral mucosa³, intestinal, renal and vascular tissues⁴ • nasal ACE2 expression correlates positively with age, being lowest at <10 years of age⁵
Immunology/ Pathogenesis	<ul style="list-style-type: none"> • current hypotheses explaining apparent disease mitigation in children are summarized⁶⁻⁸ • protective role of reduced cellular expression⁵ or higher circulating ACE2 levels in children⁹ and of “trained innate immunity”¹⁰ • Cross-reactive preexisting neutralizing antibodies against S2 subunit of SARS-CoV-2 spike protein from previous human coronavirus infections may provide protection and explain milder disease in children¹¹ • pathogenesis of Multisystem Inflammatory Syndrome in Children (MIS-C, aka PIMS-TS) related to SARS-CoV-2 involves subacute T-cell dysregulation and autoreactive antibodies^{12,13} and is distinct from classic Kawasaki disease • SARS-CoV-2 S protein displays a high-affinity binding motif similar to staphylococcal enterotoxin B and may serve as a superantigen¹⁴ • severe pulmonary disease in adults associated with cytokine storm similar to MAS/secondary HLH¹⁵ • Longitudinal evaluation of neutralizing antibody response over 90 days postinfection in adults suggests rapid decline of protective serum antibodies to SARS-CoV-2 [Seow]

<p>Transmission</p>	<ul style="list-style-type: none"> • droplet; contact $\frac{1}{2}$ life in aerosol \sim1 hour, $\frac{1}{2}$ life on plastic/steel 6-8 hours^{16,17}; detected also in patient rooms¹⁸, clinical significance unknown • viral transmission can start 1-2 days before the onset of symptoms («serial interval» < incubation period^{19,20}; recovery of virus from NPA before onset of symptoms^{21,22}) • viral RNA in NPA from children until <u>6 to >22</u> days after disease onset²³⁻²⁷ • viral RNA in feces from day <u>\sim5 to > 4 weeks</u> after disease onset^{24,26,28-31} • viral load and duration of shedding do not correlate with clinical severity in some studies^{25,26,32}, but do so in others³³ • Viable virus (culture-positive) in NPA correlates positively with RNA copy number^{34,35} • Copy number in NPA correlates inversely with age in mildly symptomatic children in one study³⁶, but not in another³⁷ • <u>vertical transmission</u>: late pregnancy transplacental passage of SARS-CoV-2 documented in one case³⁸, ending previous controversy³⁹⁻⁴⁶ • SARS-CoV-2 RNA detected in milk of an infected mother and her newborn infant⁴⁷
<p>Incubation period</p>	<ul style="list-style-type: none"> • 4-6 days (range, 1 to >14 days) • presymptomatic transmissibility 1-2 days • relapse or reinfection? Recurrent symptoms and shedding of RNA 1 month after primary infection reported in a pediatric case⁴⁸
<p>Epidemiology</p>	<ul style="list-style-type: none"> • basic reproduction rate R_0 2.2 (90% CI, 1.4-3.8)^{49,50} • high risk for «superspreader events» (dispersion parameter $k \downarrow$)⁵⁰ • <u>Switzerland</u>: confirmed cases age <10 years, 0.8%; age 10-19 years, 6.8% of all cases; 1st wave seroprevalence in Geneva 0.8% < 10 years vs. 9.1% > 10 years⁵¹ • <u>Sweden</u>: age <10 years, 0.5%; age 10-19 years 1.3% of all cases • <u>Germany</u>: survey on hospitalized children infected with SARS-CoV-2 • <u>Spain</u>: 0.8% of COVID-19 positive persons were <18 years of age⁵²; SARS-CoV-2 seroprevalence increasing with age⁵³ • transmission to children mainly within families^{24,25,29,52,54,55} • studies suggest that subclinical infection in addition to reduced susceptibility to infection contributes to lower case numbers in children^{56,57} • children less likely to be index cases in household transmission⁵⁷⁻⁵⁹ [Zhu] • Herd immunity threshold expected to be needed for SARS-CoV-2 estimated at 60%⁶⁰ <p>School, day care and household transmission</p> <ul style="list-style-type: none"> • US study suggests that school closure was associated with 62% decline in COVID-19 incidence and 49% decline in mortality⁶¹; robustness of this analysis is critically reviewed in an editorial comment⁶²

	<ul style="list-style-type: none"> • Studies find low secondary attack rates (SAR) from children in school (0.5%) and day care settings (1.2%)⁶³⁻⁶⁵ and among household contacts (HHC)^{59,66-68} • Child care-acquired infection with subsequent transmission to household contacts documented⁶⁹
<p>Clinical manifestations</p>	<p>Early disease</p> <ul style="list-style-type: none"> • common: asymptomatic^{30,70,71} • common: fever ~50-70% overall^{24,25,54,55,70,72-79} • common: cough ~50%^{24,25,55,70,74,75,78} • common: pharyngitis ~40%⁵⁵ • infrequent: diarrhea^{24,29,71,72}; 22% in Euro cohort⁷⁹ • infrequent: rhinorrhea^{55,75,78}, wheezing^{24,25,54,71,72,74,80} • infrequent: malaise, headache, myalgias • olfactory dysfunction very common in adults^{81,82} • conjunctivitis (RT-PCR positive) reported in adults⁸³ <p>Late disease</p> <p>Multisystem Inflammatory Syndrome in Children (MIS-C or PIMS-TS⁸⁴). Clusters reported in several countries (UK⁸⁵⁻⁸⁷, Italy^{88,89}, France⁹⁰⁻⁹², Spain, Switzerland⁹³, US⁹⁴⁻⁹⁸); SARS-CoV-2 PCR in NPA positive or negative; serology positive⁸⁷; various case definition reported⁸⁷</p> <ul style="list-style-type: none"> • Cardial injury typical for MIS-C increases with age⁹⁷, may involve myocardial edema⁹⁹; 36% with acute coronary abnormalities in one series¹⁰⁰ • Preliminary UK management guidelines for MIS-C available¹⁰¹ • Most common in older children and adolescents, but also reported in an infant¹⁰² • classic KD in SARS-CoV-2 positive patients reported¹⁰³ • early outcomes reported¹⁰⁴ <p>Chilblains/“COVID toe”: painful, vasculitic, frost-bite like finger/toe lesions in often otherwise asymptomatic children^{105,106}; causative role of SARS-CoV-2 questioned by some authors¹⁰⁷</p> <p>Skin eruptions: varicella-like papulovesicular rash^{108,109}; erythema multiforme¹¹⁰</p> <p>Specific organ dysfunction</p> <ul style="list-style-type: none"> • acute pancreatitis without¹¹¹ or with MIS-C¹¹² • acute rhabdomyolysis (with renal failure)¹¹³ <p>Co-infections reported in up to 50% of pediatric cases in China (most commonly <i>M. pneumoniae</i>)^{52,70,75,114}</p>

Laboratory findings	<p><u>CBC differential, CRP, chemistry uncharacteristic in mild cases</u>^{30,55,75,78,115}</p> <ul style="list-style-type: none"> leucopenia, lymphopenia and thrombocytopenia uncommon^{24,25,78,115} CRP/PCT normal to moderately elevated^{24,55,70,74,75,78,116} MIS-C: WBC↑, lympho↓, CRP↑↑, PCT↑↑, IL-6↑↑, Ferritin↑↑, NT-proBNP↑↑^{85,88,90}; Troponin↑⁸⁷
Diagnosis	<ul style="list-style-type: none"> RT-PCR from NPA; some laboratories offer quantitative copy number RT-PCR in NPA less sensitive than BAL/sputum in adults¹¹⁷ IgM/IgA appear on day ~5 of illness, IgG on day ~14^{22,118} commercial NPA rapid antigen tests available; reported sensitivity compared with PCR varies between 30% and >90%¹¹⁹ commercial serology tests available; role in clinical practice to be determined¹²⁰ Rapid antigen tests (LFA) for NP swabs commercialized by various manufacturers; Performance in adults with specificity >98%, sensitivity 85-90% compared with RT-PCR [Kaiser]. Currently no data specifically for children available.
Radiology	<ul style="list-style-type: none"> conventional CXR: normal or non-specific findings 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)^{25,55,70,74,75,121} <u>no</u> pleural effusion^{70,121} <u>no</u> hilar lymphadenopathy^{70,121}
Clinical course	<ul style="list-style-type: none"> common: asymptomatic (reported all ages)^{23-25,54} common: upper respiratory tract infection (children and healthy adults)^{24,55,78} common: pneumonia (absent, mild or moderate clinical disease)^{55,70,74,122,123} very rare: severe lung disease requiring mechanical ventilation (3/171 [1.8%] reported by Lu⁵⁵, 2 infants reported in detail⁷⁵)^{29,55,74,78} several fatal cases in SARS-CoV-2 positive infants and children reported^{55,79,124}; several deaths associated with MIS-C reported⁸⁵ infants < 1 year of age are overrepresented among hospitalized children with COVID-19 in China⁷¹, Spain⁵², US¹²⁵, Italy¹²⁶, Europe⁷⁹
Clinical course – co-morbidities	<ul style="list-style-type: none"> no specific pediatric risk factors identified to date <u>hospitalization and</u> PICU admissions more common in children with co-morbidity¹²⁷ role of ethnicity and obesity as risk factor for PIMS currently debated^{85,90,97,127-129}
Clinical course - immunodeficiency	<ul style="list-style-type: none"> <u>Primary immunodeficiency (PID):</u> severe disease appears to be rare, no deaths among patients with PID reported to POPI mild disease reported in XLA (Bruton)¹³⁰ <u>Cancer:</u> Accumulating evidence indicating <u>low risk</u> of severe disease in pediatric cancer patients in Italy, Spain¹³¹, France², Switzerland, US¹³²

	<ul style="list-style-type: none"> • <u>Transplant patients</u>: No evidence for severe disease among solid organ transplant recipients^{133,134} • <u>Autoimmune disease</u>: Benign course in children with IBD on immunomodulators and biologicals reported¹²³
Clinical course - neonates	<ul style="list-style-type: none"> • asymptomatic infection in neonates (including normal chest CT) has been reported^{29,43,70} • 3 infected neonates reported with early and short viral RNA shedding (DOL #2+4 only)¹³⁵ • complicated perinatal/postnatal courses among non-infected neonates of COVID-19 infected mothers have been reported¹³⁶
Treatment	<ul style="list-style-type: none"> • supportive • drugs with antiviral activity against ¹³⁷SARS-CoV-2 <i>in vitro</i>: remdesivir (nucleoside analog)^{138,139}, lopinavir/ritonavir¹³⁹, hydroxychloroquine¹⁴⁰ • Remdesivir reported effective in adults in one RCT¹⁴¹; no difference between 5 and 10 days of therapy in one randomized trial¹⁴² • Remdesivir recommended first line agent in children with severe disease¹⁴³ • Lopinavir/ritonavir reported ineffective in one controlled trial¹⁴⁴ • Hydroxychloroquine expected ineffective and potentially cardiotoxic in preliminary reports • Dexamethasone reported to improve outcome in a RCT in adults • immunomodulation with mAbs, e.g. tocilizumab¹⁴⁵, siltuximab (anti-IL6), azithromycin proposed to be effective against cytokine storm (RCTs in progress) • ACE2/viral entry blocker (e.g., Nafamostat) effective <i>in vitro</i>^{146,147} • recommendations against use of NSAID are NOT supported by the EMA, WHO, expert opinion¹⁴⁸

Prevention	<ul style="list-style-type: none">• Inpatients: precautions according to Swissnoso/PIGS• Outpatients: precautions according to BAG, KAZA• Neonates: no separation of well mother/child pairs needed (Swissnoso/PIGS, SGGG, WHO, DGPI, AAP); management IMC/NICU according to local infection control policy• BCG vaccine: protective effect currently debated⁷• Hydroxychloroquine ineffective in a postexposure prophylaxis RCT in adults¹⁴⁹• Dramatic decrease in pediatric ER visits¹⁵⁰⁻¹⁵², specifically for airborne viral infections^{152,153} and gastroenteritis associated with lockdown¹⁵⁴ and increase in deaths unrelated to COVID-19^{155,156}• Decrease in hospitalisations for bacterial infections during first lockdown in Israel¹⁵⁷• 90% reduction of RSV detection rate and bronchiolitis hospitalization rate in Sydney temporally associated with lockdown in Australia¹⁵⁸• Decrease in incidence of fractures associated with lockdown¹⁵⁹• Dramatic increase in diabetic ketoacidosis diagnosis in Germany during pandemic¹⁶⁰• Phase 1/2 studies using 1-2 doses of Ad5-vectored DNA vaccines¹⁶¹⁻¹⁶³ or a lipid nanoparticle-based mRNA¹⁶⁴ vaccine induce neutralizing antibodies¹⁶¹⁻¹⁶⁴, boostability¹⁶², and T-cell responses in healthy adults¹⁶¹⁻¹⁶³
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Team Kinderinfektiologie (Pediatric Infectious Disease)

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