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Steckbrief COVID-19 – Clinical characteristics in children and adolescents

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http://www.kinderklinik.insel.ch/fileadmin/Kinderklinik/Dokumente/Aktuelles/Infektiologie-COVID19-Steckbrief.pdf

Causative agent	SARS-CoV-2[1] (betacoronavirus, most closely related to SARS-CoV among the 7 human coronaviruses)
Receptor	• Angiotensin-Converting Enzyme 2 (ACE2 receptor)[2] • ACE2 expressed in upper/lower respiratory tract, oral mucosa[3], intestinal, renal and vascular tissues[4] • nasal ACE2 expression correlates positively with age, being lowest at <10 years of age[5]
Immunology/ Pathogenesis	• current hypotheses explaining apparent disease mitigation in children are summarized[6-8] • protective role of reduced cellular expression[5] or higher circulating ACE2 levels in children[9] 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 children[11] • 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 superantigen[14] • severe pulmonary disease in adults associated with cytokine storm similar to MAS/secondary HLH[15] • Longitudinal evaluation of neutralizing antibody response over 90 days postinfection in adults suggests rapid decline of protective serum antibodies to SARS-CoV-2 [Seow]

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Transmission	• droplet; contact ½ life in aerosol ~1 hour, ½ life on plastic/steel 6-8 hours[16,17]; detected also in patient rooms[18], 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 6 to >22 days after disease onset[23-27] • viral RNA in feces from day ~5 to > 4 weeks 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 others[33] • 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 study[36], but not in another[37] • vertical transmission: late pregnancy transplacental passage of SARS-CoV-2 documented in one case[38], ending previous controversy[39-46] • SARS-CoV-2 RNA detected in milk of an infected mother and her newborn infant[47]
Incubation period	• 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 case[48]
Epidemiology	• basic reproduction rate R_0 2.2 (90% CI, 1.4-3.8)[49,50] • high risk for «superspreader events» (dispersion parameter k↓)[50] • Switzerland: 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 years[51] • Sweden: age <10 years, 0.5%; age 10-19 years 1.3% of all cases • Germany: survey on hospitalized children infected with SARS-CoV-2 • Spain: 0.8% of COVID-19 positive persons were <18 years of age[52]; SARS-CoV-2 seroprevalence increasing with age[53] • 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 transmission[57-59][Zhu] • Herd immunity threshold expected to be needed for SARS-CoV-2 estimated at 60%[60] **School, day care and household transmission** • US study suggests that school closure was associated with 62% decline in COVID-19 incidence and 49% decline in mortality[61]; robustness of this analysis is critically reviewed in an editorial comment[62]

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	• 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 documented[69]
Clinical manifestations	**Early disease** • 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 cohort[79] • 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 adults[83] **Late disease** ***Multisystem Inflammatory Syndrome in Children*** (MIS-C or PIMS-TS[84]). Clusters reported in several countries (UK[85-87], Italy[88,89], France[90-92], Spain, Switzerland[93], US[94-98]); SARS-CoV-2 PCR in NPA positive or negative; serology positive[87]; various case definition reported[87] • Cardial injury typical for MIS-C increases with age[97], may involve myocardial edema[99]; 36% with acute coronary abnormalities in one series[100] • Preliminary UK management guidelines for MIS-C available[101] • Most common in older children and adolescents, but also reported in infants[102] • classic KD in SARS-CoV-2 positive patients reported[103] • early outcomes reported[104] • black and Hispanic ethnicity overrepresented[105] ***Chilblains/"COVID toe"*:** painful, vasculitic, frost-bite like finger/toe lesions in often otherwise asymptomatic children[106,107]; causative role of SARS-CoV-2 questioned by some authors[108] ***Skin eruptions:*** varicella-like papulovesicular rash[109,110]; erythema multiforme[111] ***Specific organ dysfunction*** • acute pancreatitis without[112] or with MIS-C[113] • acute rhabdomyolysis (with renal failure)[114] • large vessel arterial stroke reported [Appavu]

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	Co-infections reported in up to 50% of pediatric cases in China (most commonly *M. pneumoniae*)[52,70,75,115]
Laboratory findings	CBC differential, CRP, chemistry uncharacteristic in mild cases[30,55,75,78,116] • leucopenia, lymphopenia and thrombocytopenia uncommon[24,25,78,116] • CRP/PCT normal to moderately elevated[24,55,70,74,75,78,117] • **MIS-C:** WBC↑, lympho↓, CRP↑↑, PCT↑↑, IL-6↑↑, Ferritin↑↑, NT-proBNP↑↑[85,88,90]; Troponin↑[87]
Diagnosis	• RT-PCR from NPA; some laboratories offer quantitative copy number • RT-PCR in NPA less sensitive than BAL/sputum in adults[118] • IgM/IgA appear on day ~5 of illness, IgG on day ~14[22,119] • commercial NPA rapid antigen tests available; reported sensitivity compared with PCR varies between 30% and >90%[120] • commercial serology tests available; role in clinical practice to be determined[121] • 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	• 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)[25,55,70,74,75,122] • no pleural effusion[70,122] • no hilar lymphadenopathy[70,122]
Clinical course	• common: asymptomatic (reported all ages)[23-25,54] • common: upper respiratory tract infection (children an healthy adults)[24,55,78] • common: pneumonia (absent, mild or moderate clinical disease)[55,70,74,123,124] • very rare: severe lung disease requiring mechanical ventilation (3/171 [1.8%] reported by Lu[55], 2 infants reported in detail[75])[29,55,74,78] • several fatal cases in SARS-CoV-2 positive infants and children reported[55,79,125]; several deaths associated with **MIS-C** reported[85] • infants < 1 year of age are overrepresented among hospitalized children with COVID-19 in China[71], Spain[52], US[126], Italy[127], Europe[79]
Clinical course – co-morbidities	• no specific pediatric risk factors identified to date • hospitalization and PICU admissions more common in children with co-morbidity[128] • role of ethnicity and obesity as risk factor for PIMS currently debated[85,90,97,128-130] • A large US pediatric health system based analysis reveals similar likelihood of testing positive, but an increased risk severe COVID (OR, 5.99) in patients with co-morbidity (age 0-24 years)[131]

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	• A metaanalysis of 42 studies identifies an increased risk for severe disease (relative risk ration, 1.79) for children with co-morbidity[132]
Clinical course - immunodeficiency	• Primary immunodeficiency (PID): severe disease appears to be rare, no deaths among patients with PID reported to IPOPI • mild disease reported in XLA (Bruton)[133] • Cancer: Accumulating evidence indicating low risk of severe disease in pediatric cancer patients in Italy, Spain[134], France[2], Switzerland, US[135] • Transplant patients: No evidence for severe disease among solid organ transplant recipients[136,137] • Autoimmune disease: Benign course in children with IBD on immunomodulators and biologicals reported[124]
Clinical course - neonates	• 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)[138] • complicated perinatal/postnatal courses among non-infected neonates of COVID-19 infected mothers have been reported[139]
Treatment	• supportive • drugs with antiviral activity against [140]SARS-CoV-2 *in vitro*: remdesivir (nucleoside analog)[141,142], lopinavir/ritonavir[142], hydroxychloroquine[143] • Remdesivir reported effective in adults in one RCT[144]; no difference between 5 and 10 days of therapy in one randomized trial[145]; reported ineffective in the Solidarity trial[146] • Lopinavir/ritonavir reported **ineffective** in one controlled trial[147] • Hydroxychloroquine expected ineffective and potentially cardiotoxic • Dexamethasone reported to improve outcome in a RCT in adults • immunomodulation with mAbs, e.g. tocilizumab[148], siltuximab (anti-IL6), azithromycin proposed to be effective against cytokine storm (RCTs in progress) • ACE2/viral entry blocker (e.g., Nafamostat) effective in vitro[149,150] • recommendations against use of NSAID are **NOT** supported by the EMA, WHO, expert opinion[151]

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Prevention	• 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 debated[7] • Hydroxychloroquine ineffective in a postexposure prophylaxis RCT in adults[152] • Dramatic decrease in pediatric ER visits[153-155], specifically for airborne viral infections[155,156] and gastroenteritis associated with lockdown[157] and increase in deaths unrelated to COVID-19[158,159] • Decrease in hospitalisations for bacterial infections during first lockdown in Israel[160] • 90% reduction of RSV detection rate and bronchiolitis hospitalization rate in Sydney temporally associated with lockdown in Australia[161] • Decrease in incidence of fractures associated with lockdown[162] • Dramatic increase in diabetic ketoacidosis diagnosis in Germany during pandemic[163] • Phase 1/2 studies using 1-2 doses of Ad5-vectored DNA vaccines[164-166] or a lipid nanoparticle-based mRNA[167] vaccine induce neutralizing antibodies[164-167], boostability[165], and T-cell responses in healthy adults[164-166]

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