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COVID-19 and children: medical impact and collateral damage

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Summary

Children mostly experience mild SARS-CoV-2 infections, but the extent of paediatric COVID-19 disease differs between geographical regions and the distinct pandemic waves. Not all infections in children are mild, some children even show a strong inflammatory reaction resulting in a multisystem inflammatory syndrome. The assessments of paediatric vaccination depend on the efficacy of protection conferred by vaccination, the risk of adverse reactions and whether children contribute to herd immunity against COVID-19. Children were also the target of consequential public health actions such as school closure which caused substantial harm to children (educational deficits, sociopsychological problems) and working parents. It is, therefore, important to understand the transmission dynamics of SARS-CoV-2 infections by children to assess the efficacy of school closures and paediatric vaccination. The societal restrictions to contain the COVID-19 pandemic had additional negative effects on children's health, such as missed routine vaccinations, nutritional deprivation and lesser mother-child medical care in developing countries causing increased child mortality as a collateral damage. In this complex epidemiological context, it is important to have an evidence-based approach to public health approaches. The present review summarizes pertinent published data on the role of children in the pandemic, whether they are drivers or followers of the infection chains and whether they are (after elderlies)

major sufferers or mere bystanders of the COVID-19 pandemic.

Introduction

COVID-19 and kids have a complicated relationship. On one side, the majority of infected children experience only mild disease and immunologists tried to decipher what trait of their immune reaction mediates a mild clinical outcome. On the other side, based on experience with influenza epidemics, school closures belonged to the earliest public health measures to contain the COVID-19 pandemic, resulting in major educational harm to children. Research showed that during the pre-vaccination era children were not the driver of the pandemic. However, that situation changed with mass vaccination of the adult population. In mid-2021 when 85% of the adult population of Israel was vaccinated, 40% of new infections occurred in 10–19 years old and 12% in 0- to 9-year-old children, raising the prospect of COVID-19 becoming a disease of the young unvaccinated population (Mallapaty, 2021). This raised the dilemma of the justification of vaccination in subjects that in their majority only risk mild disease. Since the COVID-19 pandemic has occurred with distinct waves associated with different virus variants, the possibility exists that children will respond differently in different waves. To illustrate this point for children, Israeli scientists compared epidemiological and clinical data for 27 000 PCR positive 0- to 9-year-old children between December 2020 and January 2021 with those from 51 000 children who became PCR positive between August and September 2021 when the alpha variant became dominant. The weekly incidence rate in children doubled between the two waves while the hospitalization rate decreased from 1% to 0.5% (Somekh *et al.*, 2021). Due to these opposing trends, the percentage of hospitalized children with severe disease forms remained with about 7% constant, hiding phenotypic differences of two virus variants with respect to transmission and pathogenicity for children. Geographical and thereby genetic differences between children might also modulate the response of children towards SARS-CoV-2 infection. The present report

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summarizes scientific data on the medical impact of COVID-19 on children and the role of children for infection transmission in the population as evidence basis for public health decisions (vaccination, school closure) affecting children.

COVID-19 in children

During the initial phase of the COVID-19 outbreak in China less than 1% of the cases occurred in children. Retrospectively, paediatricians from Wuhan studied 1400 children with exposure to COVID-19 cases. Overall, 12% of the exposed children got infected, but the clinical course was mild: 16% of the infected children showed no symptoms and fever developed in 42% of the infected children. Intubation was needed in three children who suffered from comorbidities (Lu *et al.*, 2020). From 661 Chinese COVID-19 patients living outside Wuhan, only 5% were children. Half of them showed no symptoms or only mild upper respiratory tract symptoms, another half had mild pneumonia. Virus excretion was observed in asymptomatic cases, but was of short duration (Qiu *et al.*, 2020). One hundred and fifty-seven paediatric patients from another study in Wuhan mostly had mild (38%) or moderate disease (56%). The children showed no immunological dysregulations which was frequently seen in adult patients from Wuhan and rarely demonstrated signs of systemic inflammation (Wu *et al.*, 2020).

Similarly, during the first wave in Italy, only 1% of the COVID-19 patients were children; 21% of the infected children were asymptomatic, 58% had mild disease, 11% were hospitalized, but none died (Parri *et al.*, 2020). A European consortium of paediatrician concluded that COVID-19 is rare in children. In April 2020, 582 paediatric cases of COVID-19 were registered across 25 European countries. However, out of these 62% were admitted to hospital, 8% required intensive care and four children died. Fever was the most frequent sign (65%), followed by upper (50%) and lower (25%) respiratory tract and gastrointestinal (22%) symptoms. In multivariable analyses, factors associated with severe infections were age younger than 1 month, male sex and a pre-existing medical condition. The most common source of infection was a parent (Götzinger *et al.*, 2020).

Between February 2019 and January 2021, 6300 hospitalizations of children with COVID-19 were counted in England, of which 259 were admitted to intensive care and eight children died. Hospitalization was more common among males, older children from deprived neighbourhoods and non-White ethnicities (Ward *et al.*, 2021). Paediatricians were concerned that children suffering from chronic respiratory infection showed increased susceptibility to COVID-19 disease. For example, among

0.75 million children in Scotland aged 5–17 years, 8.4% have clinician-diagnosed asthma. Within this subpopulation, 6.8% of children had RT-PCR confirmed SARS-CoV-2 infection of whom 1.5% were admitted to hospital for COVID-19, only slightly more than in control children where 5.8% had a confirmed infection, and 0.9% were admitted to hospital. However, children with poorly controlled asthma had a sixfold higher risk for hospitalization with COVID-19 than controls (Shi *et al.*, 2021).

In April 2020, 13% of paediatric patients hospitalized in New York City tested positive for SARS-CoV-2. Fever (80%) and respiratory symptoms (64%) were the most prominent signs. A minority showed gastrointestinal symptoms (14%). Infants were less likely to show respiratory distress than older children (7% vs. 44%); 32% of the patients needed a respiratory support, 18% even mechanical ventilation. Obesity was associated with more severe disease (Zachariah *et al.*, 2020). After the first US infection wave, CDC noted that the rate of hospitalization among children is low compared with that in adults (8 vs. 165 per 100 000). While children have lower rates of mechanical ventilation and death than adults, one in three children hospitalized with COVID-19 in the United States were admitted to intensive care. Current evidence suggests that children with genetic, neurologic or metabolic conditions, children with congenital heart disease and children with obesity, diabetes, asthma or chronic lung disease, sickle cell disease or immunosuppression might be at increased risk for severe illness. Hospitalization rates in the United States are higher among Hispanic and black children compared with white children (Centers for Disease Control and Prevention, 2020). The American Academy of Pediatrics reported in September 2020 more than half a million cases of COVID-19 in US children, accounting for 10% of all US COVID-19 cases. Children represented 0.6% to 3.6% of all reported COVID-19 hospitalizations. The hospitalization rate for infected children varied widely across geographical locations ranging from 0.3% (North Dakota) to 8.3% (New York City), but death was rare (American Academy of Pediatrics, 2020).

A US study compared children with COVID-19 and influenza virus infection: 17% of COVID-19 patients and 21% of influenza patients required hospitalization; 6% and 7%, respectively, were admitted to intensive care; and 3% and 2%, respectively, required mechanical ventilation. Children hospitalized with COVID-19 were older than those admitted with influenza (10 vs. 4 years). The data indicate that COVID-19 in children is rare compared with adults, but those children affected suffer from it as much as from influenza (Song *et al.*, 2020). A comparable study was done in France with a retrospective, nationwide cohort comparing COVID-19 with seasonal influenza hospitalizations. A total of 45 800 patients

were hospitalized for seasonal influenza in 2018/2019, while 89 500 were hospitalized for COVID-19 during the spring 2020 wave. Paediatric cases were significantly more frequent with influenza than with COVID-19 (20% vs. 1.4% in subjects younger than 18 years). Overall, 1227 children were hospitalized for COVID-19 compared with 8942 children hospitalized for influenza. However, intensive care in patients younger than 5 years was more common in cases of COVID-19 than influenza (2.3% vs. 0.9%). In patients aged 11–17 years, in-hospital mortality was ten times higher for patients with COVID-19 than for influenza (1.1% vs. 0.1%) (Piroth *et al.*, 2021).

In UK, SARS-CoV-2 infections in children were usually mild and asymptomatic and accounted for a very low proportion of all COVID-19-associated hospitalizations and deaths. To guide future shielding policies for children, scientists analysed the National Child Mortality Database. Between March 2020 and February 2021, 3105 children in England died of all causes. Of these, 61 children had a concomitant positive SARS-CoV-2 test. An expert clinician panel diagnosed that 22 children died of acute COVID-19 and three of paediatric inflammatory multisystem syndrome. During this time period, 470 000 children were infected with SARS-CoV-2, giving an infection fatality rate of five per 100 000 infected children (0.005%). Thus, SARS-CoV-2 contributed just 0.8% of the 3105 childhood deaths from all causes. The authors of this study concluded that the risk of removal of children from their normal activities across education and social events might represent a greater risk than that of SARS-CoV-2 itself (Smith *et al.*, 2021).

In adult COVID-19 patients, a persistence of symptoms is reported in a sizable subgroup of patients (“long covid”). A prospective UK study determined symptom duration in 1700 children with positive SARS-CoV-2 test results. Median illness duration was 6 days and the most common symptoms were headache (62%) and fatigue (55%). 4.4% of the children reported symptoms at day 28 (compared with 13% of infected adults); symptoms were more common in older than younger children. Major symptoms were fatigue (84%), headache and anosmia (78%). Only 1.8% of the children (compared with 4.5% of the infected adults) reported symptoms at day 56, mainly anosmia. In children with respiratory symptoms, but a negative SARS-CoV-2 test, less than 1% showed symptoms at day 28 (Molteni *et al.*, 2021).

Substantial regional differences were measured for COVID-19-associated morbidity and mortality. In an international study of 10 000 children presenting at emergency departments with acute infection symptoms, 31% tested positive for SARS-CoV-2 (median age was 3 years). Of them 21% were hospitalized, 3.3% had a severe outcome and 0.1% died. Risk factors for severe

infection were age >10 years and prior pneumonia. Severe outcome rates differed substantially between countries (Funk *et al.*, 2022). A greater impact of paediatric COVID-19 has been reported in low- and middle-income countries. Between February 2020 and January 2021, 1.1 million cases were registered in Brazil of which 7.3% occurred in children. The most frequent symptoms in children were fever, cough, respiratory distress and dyspnoea. Respiratory distress was strongly associated with low oxygen saturation. A total of 11 000 cases of laboratory-confirmed paediatric COVID-19 were analysed in detail: median time from symptom onset to hospitalization was 3 days, 24% were admitted to intensive care, 10% required invasive ventilation and 7.6% died in the hospital at a median 6 days after admission. In-hospital mortality was higher during the first quartile (12%) than in later quartiles (6%). The risk of death was higher in children younger than 2 years and in teenagers than in children 2–12 years of age. The risk of death was significantly higher in indigenous children living in poor regions (Oliveira *et al.*, 2021).

A prospective surveillance study was conducted in Tamil Nadu, a 3.2 million inhabitant district of India. Overall, 440 000 RT-PCR tests were evaluated between May and October 2020 and 3.6% SARS-CoV-2 infections were identified. When young adults of 20–24 years of age were taken as reference, the odds of a positive symptomatic PCR test were 0.6 for children younger than 14 years and increased gradually for older adults, reaching odds of 2.4 compared with young adults. Asymptomatic positive PCR tests were observed with similar frequency in children and in young adults. Case fatality rates (CFR) were 0.5% for children in the age groups 0–9 years and 10–19 years and did not differ from that of young adults while CFR increased to 10% in subjects older than 89 years. CFR in Indian children was 50-fold higher than measured for children in industrialized countries. The researchers measured a 40% seroprevalence of SARS-CoV-2 IgG antibodies; the prevalence increased moderately in older children. The infection fatality rate (IFR) for 15–19 years old was with 0.002% comparable to that measured in industrialized countries and increased to 0.2% in Indians older than 70 years, fivefold lower than in industrialized countries (Laxminarayan *et al.*, 2021).

Multisystem inflammatory syndrome in children

Not all paediatric COVID-19 cases are mild. A series of cases resembling Kawasaki disease (KD), a rare vasculitis that in severe forms causes an aneurysm (dilation) of coronary heart arteries, was observed first in children from Italy (Verdoni *et al.*, 2020), France (Toubiana *et al.*, 2020) and UK (Riphagen *et al.*, 2020), but then also in

the US and elsewhere as a sequel to SARS-CoV-2 infections. The incidence of this new syndrome, now called Pediatric Inflammatory Multisystem Syndrome (PIMS) or Multisystem Inflammatory Syndrome in Children (MIS-C), was unusually high compared with KD. The affected children were older (7 vs. 3 years in KD), had higher involvement of the heart and showed macrophage activation syndrome, a hyperinflammatory state also observed in adult COVID-19 patients. The French and UK patients comprised many children from Sub-Saharan African or Caribbean origin (KD cases cluster in East Asia), raising the possibility of a distinct genetic disposition.

Subsequently, 58 British children with MIS-C were described over less than a month of observation. All children showed fever and half of them displayed gastrointestinal symptoms or rash and conjunctivitis. Many developed shock and 14% had coronary artery aneurysm (Whittaker *et al.*, 2020). British epidemiologists identified 712 hospitalizations with MIS-C, of which 312 were admitted to intensive care and five died (Ward *et al.*, 2021).

In New York State, 100 MIS-C cases followed the peak of laboratory-confirmed SARS-CoV-2 infections by 1 month, suggesting a late complication of the acute infection. Elevated levels of C-reactive protein (inflammation), d-dimer (coagulopathy) and troponin (myocarditis) were found in the affected children. Eighty per cent were admitted to an intensive care unit, and two children died. The median length of hospital stay was 6 days. The only risk factors identified for MIS-C were obesity and black race (Dufort *et al.*, 2020).

CDC identified further 186 patients with MIS-C in 26 US states: 70% of the patients had a laboratory-proven SARS-CoV-2 infection; 71% of the children had involvement of at least four organ systems, namely, the gastrointestinal, cardiovascular, haematological, mucocutaneous and respiratory system. Most children needed intensive care with intravenous immunoglobulin (100%), glucocorticoid (50%) and mechanical ventilation (20%) treatment; 2% died. A hyperinflammatory state was documented by clinical chemistry (Feldstein *et al.*, 2020). Many US children with MIS-C showed abnormal interferon signalling and increased IL-6 and IL-10 production, suggesting immunological dysregulation (Cheung *et al.*, 2020).

The pathogenesis of this severe form of paediatric COVID-19 is not clear. Swedish researchers conducted a system-level proteome, immune cell, cytokine and autoantibody analysis in children with MIS-C, children with mild COVID-19, children with KD and adults with cytokine storm and severe COVID-19. Overlaps of MIS-C with KD were found, but also differences: MIS-C patients showed less involvement of IL-17

hyperinflammation, which is characteristic for KD, and a more diffuse set of autoantibodies than KD patients. Autoantibodies in MIS-C are directed against proteins involved in immune cell signalling, and against structural proteins in heart and blood vessels. The autoimmune aspect of MIS-C is also demonstrated by the efficacy of intravenous immunoglobulin treatment which activates inhibitory F_c-receptors and thus prevents deposition of membrane-attack complexes by complement. Treatment of MIS-C is currently by intravenous IgG, corticosteroids (for general immunosuppression) and Anakinra, a recombinant IL-1-receptor antagonist (Consiglio *et al.*, 2020).

Surveillance data of 200 patients hospitalized with MIS-C who received intravenous immune globulin (IVIG) plus glucocorticoids, as compared with IVIG alone, showed that the combined treatment was associated with a lower risk of cardiovascular dysfunction than IVIG alone (17% vs. 31%) (Son *et al.*, 2021). However, a cohort study of 614 children with suspected MIS-C from 32 countries treated with IVIG alone, with IVIG plus glucocorticoids or with glucocorticoids alone found no difference between these primary treatment modes (McArdle *et al.*, 2021).

Immunology

Researchers suspected that distinct immune responses against SARS-CoV-2 could explain why some children develop MIS-C and why most children experience asymptomatic or mild infections.

When investigating MIS-C cases, researchers observed a striking elevation in multiple cytokine families, particularly for interleukin IL-6, chemokines that recruit natural killer NK cells and T cells from the circulation and cytokines potentiating mucosal immunity, such as IL-17A. Cytometry data suggest extravasation (leakage out of vessels) of T- and NK-lymphocytes as well as activation and chemotaxis of neutrophils. When the sera were analysed on a microarray, they detected IgG and IgA antibodies directed against auto-antigens, including antigens enriched in organ systems central to the pathology of MIS-C (Gruber *et al.*, 2020).

German researchers conducted single-cell RNA sequencing studies in 200 000 cells of the upper airways obtained from 42 children and 44 adults, who were either infected with SARS-CoV-2 or uninfected. They were interested to find correlates for the milder infection course in children compared with adults. Immune cells were frequently found in the nasal tract of children, but rarely in adults. Even in uninfected children, epithelial cells showed a high basal expression level of the pattern recognition receptors MDA5 and RIG-I compared with adults, which would allow immediate sensing of the infecting SARS-CoV-2. Interferon-stimulated genes were

indeed quickly detected in infected children and a stronger immune–epithelial cell cross-talk was observed in children compared with adults. The researchers also identified in children a specific subpopulation of cytotoxic T cells and a CD8⁺ T-cell population with a memory phenotype, indicating that the nasal mucosa of children is already pre-activated and primed for virus sensing. In this study, the expression level of ACE2, TMPRSS2 and FURIN, proteins involved in virus entry into cells, did not differ between children and adults (Loske *et al.*, 2021). This contrasts with an earlier study that analysed the expression of the viral receptor ACE-2 in a cohort recruited for asthma. There, young children showed significantly lower expression than older children and those again lower levels than adults even when adjusted for sex and asthma diagnosis (Bunyavanich *et al.*, 2020). Based on the activated innate immunity in children, one could expect that infected children show lower viral loads than infected adults. This was not the case: while US children showed a lower percentage of symptomatic infections than adults (62% vs. 93% of PCR-positive subjects) and a 1-day shorter disease duration, the viral load estimated from C_t PCR threshold values did not differ between symptomatic children and symptomatic adults. Asymptomatic children showed lower viral loads than symptomatic children, but again these values were not different from those of asymptomatic adults (Chung *et al.*, 2021). Another report also noted comparable viral loads in symptomatic 5- to 17-year-old children and in symptomatic adults, but significantly higher viral loads in symptomatic children younger than 5 years (Heald-Sargent *et al.*, 2020).

US immunologists conducted a detailed “systems serology” study in children with mild COVID-19, in adults with mild or severe disease and children with MIS-C. High titres of SARS-CoV-2 spike protein (S)-specific IgM, IgG and IgA were observed in adults with severe infection. S-specific IgG and IgM levels were similar in children and adults with mild disease, but significantly lower compared with adults with severe disease. IgG attenuated neutrophil phagocytosis, while enhanced inflammatory neutrophil activity was observed in the presence of SARS-CoV-2-specific IgA. The data implicate IgA-driven functions in severe disease that do not evolve in children or adults with mild disease. Children who developed MIS-C showed inflammatory monocyte-activating SARS-CoV-2 IgG antibodies, with antibody levels similar to those in convalescent adults. IgG alone might be sufficient to control the infection and lead to mild symptoms, while serum IgA emerged in this study as a highly potent activator of innate immune effector functions. The authors suggest that IgA and monocyte-activating antibodies play an unsuspected pathological role in COVID-19 and in MIS-C (Bartsch *et al.*, 2021).

British immunologists described broadly similar antibody responses in children and adults with mild disease. Seroconversion in children also boosted responses against seasonal Beta-coronaviruses through cross-recognition of the S2 domain of the spike protein, while neutralization of viral variants was comparable between children and adults. Spike-specific T-cell responses were higher in children than in adults and were also detected in many seronegative children, indicating pre-existing cross-reactive responses to seasonal coronaviruses. In addition, children maintained antibody and cellular responses longer than 12 months, while adults showed a waning immune response at 6 months (Dowell *et al.*, 2022). German immunologists who analysed the immune response in 550 children and 700 adults observed no significant difference in antibody response between symptomatic and asymptomatic infections both for children and adults (Renk *et al.*, 2022).

US immunologists identified B-cell memory cells in the blood of pre-COVID-19 pandemic individuals with specificity to SARS-CoV-2, indicating prior antigen experience. They derived from these cells monoclonal antibodies that showed over 90% blocking of ACE2 binding by SARS-CoV-2. In comparison with adults, children had higher frequencies of pathogen-specific B-cell clones in the blood and the researchers hypothesized that previous seasonal human coronavirus exposures may stimulate cross-reactive memory cells that might explain the frequently observed asymptomatic infection with SARS-CoV-2 in children (Yang *et al.*, 2021). SARS-CoV-2-reactive antibodies were found in uninfected individuals and were particularly prevalent in children and adolescents. These IgG antibodies target epitopes in the S2 segment of the viral spike protein (the receptor-binding domain of the viral spike is located in the S1 segment). Since these antibodies neutralized SARS-CoV-2 and because S2 shares similarity across different coronaviruses, this observation points to the possibility of a universal vaccine against many coronaviruses. This observation might also explain the mild infections in children since they experienced more and recent exposure to seasonal coronavirus compared with adults (Ng *et al.*, 2020).

Vaccination

From the distinct immune reaction of children towards natural SARS-CoV-2 infection, one might also suspect a distinct immune reaction towards vaccination compared with adults. This was not the case for Chinese 3- to 17-year-old children receiving the inactivated SARS-CoV-2 vaccine CoronaVac together with alum adjuvant in two intramuscular doses. In phase 1 and 2 trials enrolling 550 children, adverse reactions consisted mainly of

injection site pain and children showed a nearly 100% seroconversion rate for neutralizing antibodies across the whole age range tested in a vaccine dose-dependent way (Han *et al.*, 2021). Phase 1/2 trials with the inactivated BBIBP-CorV vaccine in 1000 Chinese children ranging in age from 3 to 17 years also showed only mild adverse reactions (injection site pain and fever) and very high seroconversion rates for all age groups with significantly higher neutralizing antibody titres with the 4 µg than the 2 µg dose (Xia *et al.*, 2021).

A total of 2260 adolescents, 12–15 years of age, received 30 µg of the Pfizer BioNTech mRNA vaccine or placebo. Adverse reaction consisted of transient injection site pain, fatigue and headache. One vaccinee experienced 40.4°C fever. The adolescent vaccinees showed a nearly twofold higher neutralizing antibody titre than young adults receiving the same vaccine and none of the 1000 vaccinated adolescents experienced COVID-19 disease after the second injection compared with 16 COVID-19 cases in 980 placebo recipients, indicating a 100% vaccine efficacy (Frenck *et al.*, 2021).

After a dose-finding phase 1 test, the dose of 10 µg of the mRNA vaccine from Pfizer-BioNTech was chosen for a phase 2/3 randomized and placebo-controlled trial in 2300 children. Adverse effects consisted of pain at the injection site and fatigue and headache for 1 or 2 days. Ninety-nine per cent of the 5- to 11-year-old children achieved an antibody response after the second dose and the neutralization titres were comparable to those of young adults. At 2 months of follow-up after the second dose in the summer 2021, 3 vs. 16 COVID-19 cases were observed in the vaccinated and placebo recipients, respectively, corresponding to a 90% vaccine efficacy. The test was conducted in the US and different European countries (Walter *et al.*, 2022). Because children experience mostly mild infections and motivation to vaccinate children is to facilitate their educational and social life and to contribute to herd immunity for pandemic control in the whole population, the safety of paediatric coronavirus vaccines is important. The Pfizer-BioNTech mRNA vaccine was authorized in the US on May 10, 2021, for emergency use in children aged 12 years and older. Since then, children were screened for adverse events linked to vaccination. The Boston Children's Hospital observed 15 cases of myocarditis which occurred within a week after vaccination. The typical case was a 15-year-old boy after the second vaccine dose. Symptoms were chest pain, fever, myalgia and headache. The patients were only mildly affected, none needed intensive care and in 73% of cases symptoms resolved during 2 weeks after hospital discharge (Dionne *et al.*, 2021). In Israel, 400 000 mRNA-vaccinated adolescents were followed for myocarditis: 15 cases were observed, most occurred after the second dose in males.

An incidence of one case of myocarditis per 12 000 male adolescents and 0.7 cases for 100 000 female adolescents was estimated. All cases were clinically mild (Mevorach *et al.*, 2022).

US paediatrician noted that a quarter of the U.S. population is under 18 years old and effective herd immunity in the US will require paediatric vaccination (Klass and Ratner, 2021). Other scientists questioned these conclusions and the need of childhood vaccination and asked whether children are really in the herd. They argued that the herd argument is only relevant if children are not only recipients of the infection from adults, but also the source of infection for adults (Obaro, 2021). This discussion can only be settled by epidemiological data investigating the role of children in infection susceptibility and transmission.

Household transmission

An early seroprevalence study from March 2020 in Geneva/Switzerland with 2700 participants showed that children are not the driver of the epidemic: only one out of 123 children, 5–9 years old, had antiviral antibodies. This rate increased to adult levels of about 10% in adolescents (Stringhini *et al.*, 2020). A parallel serosurvey of 4400 households from Geneva showed that children < 10 years had a threefold lower risk of infection from household members than middle-aged adults. In contrast, 10- to 19-year-old children had a similar risk of infection as adults, while subjects older than 65 years, the vulnerable population for severe disease, displayed a threefold higher household infection risk (Bi *et al.*, 2021). A study from South Korea evaluated 107 paediatric index cases and the occurrence of secondary infections in 248 household members. Overall, 41 infections were observed in household members, but 40 of them shared the same exposure history as the index case, making household transmission unlikely. Only one secondary household infection was documented that was definitively transmitted from a child (Kim *et al.*, 2021). Greek epidemiologists concurred with this conclusion: when studying 23 clusters where at least one child was in the household, transmission of infection occurred from an adult to a child in 19 clusters and from an adult to another adult in 12 clusters (Maltezou *et al.*, 2021). Epidemiologists from Israel concluded that children are not effective spreader of infection because in 12 of the 13 families living under crowded conditions, the first diagnosed member was a parent (Somekh *et al.*, 2020). In contrast, a study from two US states observed that transmission of SARS-CoV-2 within households is high, occurs quickly and can originate from both children and adults. Prompt adoption of disease control measures, including self-isolating at home and wearing a mask by

all household members in shared spaces, can reduce the probability of household transmission (Grijalva *et al.*, 2020). However, another study from the US came to a different conclusion: the percent contribution to onward spread was 41% from individuals aged 35–49 years, followed by 35% from the 20–34 years young adults, while children contributed just 2% and teenagers 4% to the forward infections (Monod *et al.*, 2021).

Several studies also documented that children were less likely infected from index cases in the household. When analysing 30 000 primary cases from Wuhan during the early phase of the COVID-19 epidemic for secondary transmission to about 60 000 identified household contacts, a 16% transmission rate was observed. Subjects < 20 years represented 1.4% of the primary and 4.8% of the secondary cases. Individuals aged 60 years or older were the most susceptible age group to SARS-CoV-2 infection. The least susceptible age group was children aged 2–5 years. The transmission model estimated that individuals younger than 20 years were about 75% less susceptible than older adults. However, cases younger than 20 years were more likely to infect others than cases older than 60 years, which was explained by a higher contact rate with children than elderlies. Asymptomatic individuals were fivefold less likely to infect others than symptomatic cases. Symptomatic cases in turn were more likely to infect others before symptom onset than after symptom onset (Li *et al.*, 2021). In another study from Hunan province/China with 1200 index cases and 15 000 contacts, the risk of transmission in the household increased during the lockdown period reflecting the intensified contacts at home. Children aged 0–12 years were significantly less susceptible to infection than individuals 26–64 years (odds ratio 0.41); while subjects older than 65 years were significantly more susceptible (odds ratio 1.39) to infection (Sun *et al.*, 2021). In another study from China, 105 index cases with moderate COVID-19 and 392 household contacts were investigated for secondary transmission: 64 contacts (16%) were infected mostly with moderate disease. Time to secondary infection was 6 days. The transmission probability was age dependent: 4% in children and 17% in adults. Spouses experienced 28% infection transmission (Li *et al.*, 2020).

After a COVID-19 outbreak among children and adolescents on a camp site, the infected and mostly symptomatic campers transmitted the infection to 18% of their families after returning home. Keeping physical distance or wearing always masks reduced the infection probability by half (Chu *et al.*, 2021). Canadian researchers identified paediatric index cases in 7% of 89 000 households from Ontario that were investigated during the second half of 2020. When analysing 6000 households with paediatric index cases, 27% of the households experienced

secondary infections. Children aged 0–3 years had the highest odds of transmitting SARS-CoV-2 to household contacts (odds ratio, 1.43 compared with 14- to 17-year-old children). Paediatric index cases with and without symptoms reported similar transmission rates. Although children do not appear to transmit infection as frequently as adults, caregivers should apply infection control measures, such as use of masks, increased hand washing and separation from siblings (Paul *et al.*, 2021).

British epidemiologists investigated whether living with children increased the SARS-CoV-2 infection and COVID-19 hospitalization risk in adults from the same household. During the first epidemic wave, no increased infection and disease risk were seen, while during the second epidemic wave, in UK a small increase (odds ratio 1.06) was observed. Risk of COVID-19 death, however, was reduced in adults living with children (Forbes *et al.*, 2021).

Epidemiology

Further epidemiological data indicate a lower susceptibility of children to infection with SARS-CoV-2. Contact surveys were conducted in Wuhan and Shanghai during the height of the epidemic in China (February 2020). From these data, it was deduced that children (<14 years) had only a third as high infection rate as adults, while older individuals had a 50% higher infection rate (Cobey, 2020). In Shenzhen/China where 8% of close contacts of 390 index cases got infected during Spring 2020, the infection risk was comparable for all age groups, but half of the infected children showed no fever (Bi *et al.*, 2020). A detailed population-wide survey was conducted in a small town during the Spring 2020 wave in severely affected Northern Italy. No infections were detected in children < 10 years of age, including those living in a household with an infected person, while for adults the risk of infection from an infected household member was very high (Lavezzo *et al.*, 2020). Likewise, when a representative sample of 11 000 subjects from Iceland were tested in March 2020, 0.8% were positive for SARS-CoV-2 RNA. The highest prevalence was seen in 40-year-old subjects, while no children under 10 years were infected. Furthermore, 13% of 9000 high-risk subjects (contacts with infected persons, or travel history to outbreak areas) were positive for viral RNA. Children under 10 years showed a 7% prevalence rate compared with 14% in subjects older than 10 years (Gudbjartsson *et al.*, 2020). Among children, adolescents and young adults in the US, weekly incidence increased with age. Time trends in children and adolescents tracked consistently with trends observed among adults. Reported incidence and positive test results among children aged 0–10 years were consistently lower than those in older age

groups, suggesting that children are following and not leading the infection process (Leidman *et al.*, 2020).

About 27 000 children were tested for SARS-CoV-2 serum antibodies between January 2020 and February 2021. Seroprevalence increased from the first wave (0.7%) to the second wave (3.9%). The increase was explained by the winter occurrence of the second wave, school openings and more infectious variants (B.1.1.7). Seroprevalence was higher in school than in pre-school children (5.6 vs. 8.4% in February 2021) and about four-fold higher than PCR-positivity rates in children. However, 68% of seropositive pre-school and 51% of school children reported no symptoms (Hippich *et al.*, 2021).

These population and family transmission data are not only relevant for the question about the need to extend the vaccination to children, but also for the discussion about the need to close schools which substantially affected the social life of millions of children during the pandemic.

School closure and opening

Experience with previous influenza epidemics had shown that school closures caused an influenza case reduction between 10 and 17%. Based on these data, school closures were considered in many countries, despite a lack of epidemiological data demonstrating the efficacy of this intervention for COVID-19. Australian epidemiologists screened the literature on household transmissions of COVID-19 where 10% were identified as having a paediatric index case. In contrast, 54% of household transmission of influenza virus had children as the index case demonstrating that taking influenza as a precedence might be flawed (Zhu *et al.*, 2021). In March 2020, about half the world's student population were required to stay at home, causing enormous educational losses. British physicians doubted the effectiveness of this measure, because school closures are only meaningful during low viral transmission periods and if viral susceptibility is greater in children than in adults (Hassard *et al.*, 2021). Empirical studies from South Korea, Europe and Australia show in contrast that schools can open safely when community transmission is low. In New South Wales/Australia, only 25 of the 7700 schools or day-care centres reported a primary infection and only four facilities had onward transmission. In the neighbouring state of Victoria having higher community transmission rates, hotspots were also identified in schools. In Israel which showed a high community transmission, an outbreak occurred at a school affecting 153 students and 25 staff members, and was further transmitted to 87 family members. Transmission was facilitated by more than 30 children per classroom and a heatwave compromising the wearing of masks

(Mallapaty, 2020). Supporting evidence comes from Italy where from 65 000 schools which reopened in September 2020 only 2% of schools reported an outbreak and in 93% of cases, only one infection was notified. Most of the 30 confirmed school outbreaks which occurred in June 2020 in England involved transmission between staff members, and only two involved student-to-student spread (Lewis, 2020). During the first infection wave, Sweden kept all schools open. Swedish epidemiologists looked into the national intensive care unit register and noted no significant increase in paediatric intensive care admissions before or during the first wave (Ludvigsson *et al.*, 2021). German paediatricians investigated 2500 children (mean age 6 years)–parent pairs from Southern Germany during the height of the second wave. A parent who was seropositive and the corresponding child seronegative ($n = 34$) was fourfold more common than the combination of a parent who was seronegative and a corresponding child who was seropositive ($n = 8$). The data make it unlikely that children have boosted the epidemic in Germany (Tönshoff *et al.*, 2021). A US study analysed 4876 students and 654 staff members who participated to in-person learning in schools from rural Wisconsin. Among the 191 cases identified in students and staff members, only seven (3.7%) were linked to in-school transmission and no infections among staff members were found to have been acquired at school (Falk *et al.*, 2020).

In England, SARS-CoV-2 infection rates were low in primary schools following their partial and full reopening in June and September 2020 respectively. A group comprising 12 000 pupils and staff underwent weekly nasal swabs after partial school reopening in the summer half-term. According to PCR tests, one student and two teachers got infected during the observation period. At baseline, seroprevalence was 11% and 15% in pupils and teachers, respectively, similar to that observed in the general population. During the serological survey part of this study, only four students and one staff seroconverted to SARS-CoV-2, indicating a low rate infection transmission in schools (Ladhani *et al.*, 2021).

In an open-label, cluster-randomized, controlled trial in secondary schools from England, 200 schools were randomly assigned to self-isolation of school-based COVID-19 contacts for 10 days (control group) or to voluntary daily antigen testing for 7 days with negative contacts remaining at school (intervention group). Over a 10-week observation period between April and June 2021, there was a comparable number of symptomatic PCR-confirmed infections (59 vs. 62 per 100 000 participants and week) demonstrating that daily contact testing of school-based contacts was non-inferior to self-isolation for control of COVID-19 transmission. Overall the infection rates in school-based contacts were low, with very

few school contacts testing positively (Young *et al.*, 2021).

A small prospective cohort study conducted between September and December 2020, in a primary school in Belgium showed a different picture: 20% of 63 children and 27% of 112 teachers tested positive in weekly throat washings; most transmission events occurred among either teachers or among children within the school. Eight secondary infections occurred in the households and were transmitted from the school setting (Meuris *et al.*, 2021).

In a survey from Japan, municipalities with open schools were matched to municipalities with closed schools. The outcome parameter was the daily numbers of newly confirmed cases in the 800 municipalities between March and June 2020. School closures did not significantly reduce the spread of COVID-19 in the municipalities practicing school closure (Fukumoto *et al.*, 2021).

US epidemiologists conducted a retrospective nationwide cohort study evaluating the effect of schooling mode (traditional, hybrid or virtual) on SARS-CoV-2 cases in July to September 2020. Overall incidence rates were not statistically different in counties with in-person learning versus remote school learning. However, there were differences between the regions since in southern US traditional and hybrid school opening was associated with an increase in case numbers. The researchers concluded that schools can open for in-person learning during the pandemic with minimal contribution to sustained community incidence of infections, provided other public safety measures such as mask wearing are adopted (Ertem *et al.*, 2021).

In July 2021, British scientists published a systematic review of observational studies analysing the impact of school closure, school reopening and school holidays on the transmission dynamics of the epidemic. Among higher quality, less confounded studies of school closures, six out of 14 studies reported that school closures had no effect on transmission, six reported that school closures were associated with reductions in transmission and two reported mixed findings. Good-quality observational studies from Europe and the US all demonstrated that school re-openings can be successfully implemented without increasing community transmission of SARS-CoV-2, provided that baseline incidence is low and robust infection prevention and control measures are in place. A major problem for a rational assessment of the value of school closure is the absence of controlled trials and that school closure was mostly implemented together with other NPI measures such that the impact of school closure cannot easily be assessed in isolation (Walsh *et al.*, 2021).

In the US, health epidemiologists conducted a weekly online survey of 2 million households where 0.5 million

households comprised at least one child. Between December 2020 and February 2021 living in a household with a child engaged in full-time in-person schooling was associated with an increased risk of SARS-CoV-2 infection in adult family members (odds ratio 1.38). The increase in infection risk was small for children below 5 years and increased with age. No risk increase for adult household members was seen when children attended only part-time schooling. Parallel with mitigation measures implemented in schools, the infection risk for adult household members decreased. When the researchers investigated 15 different mitigation measures, teacher masking, daily symptom testing and no extracurricular activities had the greatest attenuating effect while desk shields and closed playgrounds paradoxically increased the risk (Lessler *et al.*, 2021).

During the Spring 2020 epidemic wave, Swedish upper-secondary schools moved to online instruction, while lower secondary schools remained open, realizing a quasi-experimental study design. Swedish economists evaluated the effect of this differential school closure policy on the infection risk of parents and teachers. Among parents, exposure of their children to open rather than closed schools resulted in a small increase in PCR-confirmed infections (odds ratio 1.17), while teachers working in open schools experienced a twofold higher infection risk and constitute the seventh-most affected occupation (taxi drivers were at the top of all professions). The higher incidence of infections among lower secondary teachers spilled over to their partners at home, who had a higher incidence of positive PCR tests than partners of upper-secondary teachers (odds ratio 1.29). The authors concluded that closing the schools is a costly measure with potential long-run detrimental educational and economic effects for students and that school closure is not an effective way to contain SARS-CoV-2. However, teachers in open schools need to be protected by masking, reduced class sizes and vaccination (Vlachos *et al.*, 2021).

When analysing daily electronic reports of viral test positivity in England between July and December 2020, Public Health England noted that cases in school-aged children lagged behind and followed adult trends after schools re-opened. The November lockdown was associated with declines in adult infection rates, followed a week later by declines in student cases. School children are in this analysis not drivers, but followers of the epidemic dynamics (Mensah *et al.*, 2021).

Collateral damage

Some damage to children is a direct consequence of school closure. For US pupils school achievements declined by 3-7 percentile points in reading and 9-11

points in maths by the end of the 2020–2021 school year. Others calculated that this resulted in the loss of 4–5 months of learning in that year (Anonymous, 2022). Indeed, harm of school closure in academic, health and economic terms is high. Direct costs for 12 weeks of school closure were estimated to US \$128 billion in lost productivity. Economic analyses suggest indirect costs from lost learning with projected annual income losses of 2–3% over the course of affected students' lifetimes which translates into \$2.5 trillion in the US (12.7% of annual GDP) in lost future earnings. School closures affect high- and low-income families differently, which further accentuates social differences in the next generation (Donohue and Miller, 2020). Other effects are less obvious, but nevertheless real. A US study evaluated the benefit of school closure on the COVID-19 epidemic against the decreased availability of healthcare workers who remained at home to take care of their children. From demographic data in the US, they calculated that 15% of healthcare workers could not go to work due to school closure. If in their model death rate would increase from 2 to 2.4% for COVID-19 patients due to their absence, this effect would cause a greater number of deaths than school closure would have prevented (Bayham and Fenichel, 2020). School closure also had a negative effect on food security: USDA is serving school breakfast and lunch programs to 35 million children in the US. School closure thus affected the nutrition of children from low-income US families who suffered disproportionately already from the lockdown and joblessness of their parents (Dunn *et al.*, 2020). The COVID-19 pandemic poses even graver risks to the nutritional status and survival of young children in low- and middle-income countries (LMIC). Researchers calculated in a macroeconomic model a 8% decrease in gross national income, which translates in their microeconomic model into a 14% increase in the prevalence of moderate or severe wasting (low weight-for-height) among children younger than 5 years. This adds an additional estimated 6.7 million children with wasting in 2020 and they calculated as consequence 130 000 additional deaths in children younger than 5 years during 2020, with an estimated 52% of these deaths occurring in sub-Saharan Africa (Headey *et al.*, 2020).

Women in childbearing age and neonates experience mostly mild disease, but in LMIC they might be severely affected since the epidemic interrupted essential maternal and child health interventions. Researchers calculated 250 000 additional child deaths and 12 000 additional maternal deaths over a period of 6 months under the least severe scenario of COVID-19 impact. This would increase maternal and child death rates by 10%. Child death would result from reduced antibiotic coverage for bacterial pneumonia and sepsis, lack of oral rehydration

for diarrhoea treatment and increased childhood malnutrition (Robertson *et al.*, 2020). Health metrics researchers also noted that about 9 million children missed the third-dose diphtheria–tetanus–pertussis and first-dose measles-containing vaccines mainly due to a drop in immunizations caused by COVID-19 restrictions in April 2020. This translates into a worldwide 8% decline in vaccine coverage, putting children at higher risk of infection most notably in north Africa and the Middle East, south Asia and Latin America (Causey *et al.*, 2021).

Public health scientists estimated that between March 2020 and April 2021 about 1.1 million children experienced the COVID-19-associated death of a primary caregiver. Peru and South Africa were the most hit countries with 10 and 5, respectively, deaths of a caregiver per 1000 children, followed by Mexico and Brazil. The loss of a father was more frequent than the loss of a mother. Economic support is needed to avoid the institutionalization of the affected children (Hillis *et al.*, 2021).

Some more subtle effects might only become apparent in the future. Recently, researchers reported effects of the pandemic on the brain development of young infants. Infants born during the pandemic scored lower on tests of gross motor, fine motor and communication skills compared with those born before it. The effect was independent of the infection status of the pregnant mother and might be the outcome of a psychologically stressful pregnancy (Wenner Moyer, 2022). Detrimental psychological effects were also reported for young schoolchildren. The COVID-19 pandemic has not only interrupted the education of more than 1 billion children worldwide. Beyond learning deficits resulting from school closure, psychologists observed that children's behavioural outcomes tended to be worse during remote schooling than during in-person schooling while hybrid learning fell in between (Hanno *et al.*, 2021). A review of the literature revealed higher screen time and greater social media use, resulting in lower physical activity. Many children reported anxiety and depressive symptoms and that they missed social contacts which are formative in this crucial period of social development (Viner *et al.*, 2022).

Psychological effects such as hospital fear also caused collateral damage. In Italy, only 1.5% of Covid-19 cases during the first wave occurred in children, 11% of them needed hospitalization, none had intensive care and no death was observed. During that time period paediatric hospitalization decreased substantially for fear of infection in the hospital, which caused an increased number of child deaths due to delayed arrival of children in hospitals (Lazzerini *et al.*, 2020). Similar observations were made for adults in the UK and US where deaths from dementia, asthma, diabetes and hypertension increased significantly during the pandemic for hospital fear (Viglione, 2020; Woolf *et al.*, 2020).

Outlook

Many public health decisions to curb the pandemic were initially taken without a sound scientific evidence for them. Some of them were based on past experience with influenza epidemics and it became later clear that a one-to-one transfer of data from influenza to coronavirus epidemics can be misleading. School closure decisions are problematic in this respect. While overreactions without a sound scientific basis might be problematic, underreactions by public health authorities as in the initial discouragement of mask wearing were detrimental. Both the attitude towards school closure and mask wearing and other mitigation measures have changed with the accumulation of scientific data on these subjects, albeit compromised by emotional attitudes and arguments which reflect more political prejudices than acquired pandemic insights. However, in hindsight, health authorities should not be condemned for doubtful decisions, since a new pandemic starts with a huge knowledge gap. After 2 years of pandemic, a lot has been learned but the public health dilemmas have not been solved since each infection wave with a new virus variant confronts us with new unknowns about the properties of the new virus strain, necessitating a constant check and reassessment of the efficacy of control measures. Again, the omicron wave obliges public health authorities to take decisions with limited scientific information on the epidemic behaviour of this virus. What was true for the pandemic and its control in 2020 might not necessarily be true in 2021 and 2022. Clinical and epidemiological data from the omicron wave in South Africa can illustrate this point: the highest rate of hospitalization was observed with 18% of all cases in children younger than 5 years while subjects older than 60 years contributed only 8% of the SARS-CoV-2-associated hospitalizations (Wolter *et al.*, 2022). This observation might indicate a higher susceptibility of young children to omicron-induced disease compared with previous viral variants. However, the data need to be interpreted in context: omicron-associated cases showed a 2.4% hospitalization rate during the investigated time period compared with a 12.8% hospitalization rate for non-omicron COVID-19 cases. Severe cases were also much more frequent in older subjects than in young children. When quoting scientific evidence one should therefore mention the pandemic period when they were acquired. Too highlight this one might want to speak of COVID-19, COVID-21 and COVID-22 or quote the dominant circulating virus variants as COVID-alpha, COVID-delta or COVID-omicron for shorthand notation. The effect of different mitigation measures (mask, distancing, gatherings, closures, etc.) need to be reinvestigated to provide evidence-based public health measures

for new variants behaving so differently as the omicron variant.

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Conflict of interests

None declared.

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