Long-Term Antibody Response to SARS-CoV-2 in Children

Gabor A. Dunay1 · Madalena Barroso1 · Mathias Woidy1 · Marta K. Danecka1 · Geraldine Engels1 · Katharina Hermann2 · Friederike S. Neumann1 · Jan Beime2 · Gabriele Escherich3 · Kristin Fehse1 · Lev Grinstein2 · Franziska Haniel4 · Luka J. Haupt1 · Laura Hecher2 · Torben Kehl4 · Christoph Kemen5 · Markus J. Kemper6 · Robin Kobbe7 · Aloisa Kohl7 · Thomas Klokow1 · Dominik Nörz8 · Jakob Olfe4 · Friderike Schlenker2 · Jessica Schmiesing1 · Johanna Schrum3 · Freya Sibbertsen1 · Philippe Stock2 · Stephan Tiede1 · Eik Vettorazzi10 · Dimitra E. Zazara2,11 · Antonia Zapf10 · Marc Lütgehetmann8 · Jun Oh2 · Thomas S. Mir4 · Ania C. Muntau2 · Søren W. Gersting1 • the C19.CHILD Study Group

Received: 4 March 2022 / Accepted: 18 August 2022 / Published online: 19 September 2022 © The Author(s) 2022

Abstract

Almost 2 years into the pandemic and with vaccination of children significantly lagging behind adults, long-term pediatric humoral immune responses to SARS-CoV-2 are understudied. The C19.CHILD Hamburg (COVID-19 Child Health Investigation of Latent Disease) Study is a prospective cohort study designed to identify and follow up children and their household contacts infected in the early 2020 first wave of SARS-CoV-2. We screened 6113 children < 18 years by nasopharyngeal swab-PCR in a low-incidence setting after general lockdown, from May 11 to June 30, 2020. A total of 4657 participants underwent antibody testing. Positive tests were followed up by repeated PCR and serological testing of all household contacts over 6 months. In total, the study identified 67 seropositive children (1.44%); the median time after infection at first presentation was 83 days post-symptom onset (PSO). Follow-up of household contacts showed less than 100% seroprevalence in most families, with higher seroprevalence in families with adult index cases compared to pediatric index cases (OR 1.79, \( P = 0.047 \)). Most importantly, children showed sustained seroconversion up to 9 months PSO, and serum antibody concentrations persistently surpassed adult levels (ratio serum IgG spike children vs. adults 90 days PSO 1.75, \( P < 0.001 \); 180 days 1.38, \( P = 0.01 \); 270 days 1.54, \( P = 0.001 \)). In a low-incidence setting, SARS-CoV-2 infection and humoral immune response present distinct patterns in children including higher antibody levels, and lower seroprevalence in families with pediatric index cases. Children show long-term SARS-CoV-2 antibody responses. These findings are relevant to novel variants with increased disease burden in children, as well as for the planning of age-appropriate vaccination strategies.

Keywords Pediatric · Longitudinal · Serology · Ancestral · COVID-19

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has been responsible for over five million deaths [1]. Severe disease due to acute coronavirus disease 2019 (COVID-19) is rare in children and teenagers [2–4], and the pediatric inflammatory multisystem syndrome (PIMS, also termed MIS-C) attributable to SARS-CoV-2 only occurs in a small minority of cases [5, 6]. Vaccination of adults and teenagers is now widespread even though vaccination rates show large regional differences [1]. Vaccination of younger children above the age of five years [7] has been ongoing for several months (the USA) to several weeks (Europe) and even longer in China at the time of this report. Emerging viral variants, especially the most recent omicron variant (B.1.1.52), appear to escape neutralizing antibodies provided by vaccination [8]. Furthermore, the pediatric population may be at increased risk, because initial reports of the omicron variant suggest an increased hospitalization rate in children compared to earlier variants [9].

Despite the pressing need to better understand long-term antibody responses in children, longitudinal studies over longer
periods after natural infection are almost completely lacking in this age group. Here, we present a prospective cohort study of 67 convalescent children and their household contacts including a quantitative follow-up of antibody responses in household clusters up to 9 months after symptomatic infection. The children were recruited in the C19.CHILD Hamburg Study (COVID-19 Child Health Investigation of Latent Disease), in which over six thousand children under eighteen years of age were screened for acute SARS-CoV-2 infection by PCR and 4657 serological tests were performed. The recruitment to the study followed a general lockdown after the initial wave of ancestral SARS-CoV-2 infection in 2020.

Methods

Study Population and Ethical Approval

We conducted an observational prospective multi-center cohort study of children under eighteen years of age in all five pediatric hospitals of the Free and Hanseatic City of Hamburg, Germany: AKK Altonaer Kinderkrankenhaus, Helios Mariahilf Kinderklinik, Klinik für Kinder- und Jugendmedizin der Asklepios Klinik Nord-Heidberg, Katholisches Kinderkrankenhaus Wilhelmstift, and Werner und Michael Otto Universitätskinderklinik at the University Medical Center Hamburg-Eppendorf (Kinder-UKE) from May 11 to June 30, 2020. As part of a general lockdown, school and day care facilities in Hamburg were closed from March 1 to at least May 18, 2020, so that recruitment to the study began shortly before lifting these measures. Patients presenting to the study hospitals were invited to participate. In addition, children from the community were welcomed to enroll through the C19.CHILD Study Clinic at Kinder-UKE. The study population consisted of (i) in- and outpatients aged 0 to <18 years of all pediatric hospitals in Hamburg, Germany; (ii) children aged 0 to <18 years as volunteers; (iii) participants of other studies (Prenatal Investigation of Children’s Health-PRINCE study, Hamburg City Health Study) aged 0 to <18 years; and (iv) children, who were household contacts of SARS-CoV-2 positive study participants.

For recruitment of volunteers, appeals were launched via social media and consent forms and information sheets were distributed via the websites c19child.hamburg and c19child.de. In addition, information material was distributed to schools, kindergartens, and public institutions in the Hamburg area. Filling out a standardized questionnaire, as well as taking a nasopharyngeal swab for the PCR detection of SARS-CoV-2 RNA, was obligatory for all participants during the screening phase, whereas a venous blood draw for the detection of antibodies directed against SARS-CoV-2 was optional.

Recruitment and consent procedures were equivalent in all participating hospitals. A written informed consent was obtained for each participating subject. A written informed consent was obtained from parents or guardians in all cases, from children over 7 years whenever possible; for children, also consent in spoken word was accepted. The inclusion criteria were as follows: (i) children or teenagers aged 0–18 years; (ii) patient in one of the participating centers or volunteer in the central C19.CHILD Study Clinic; (iii) informed consent from parents or guardians; (iv) informed consent from children >7 years (unless not capable). The exclusion criteria were as follows: (i) prematurity <37 weeks of gestation; (ii) informed consent of parents or guardians not possible in spoken word or otherwise; (iii) informed consent not given. The study was approved by the local ethical committee of Hamburg (reference number: PV7336) and published at clinicaltrials.gov (NCT04534608).

Children with a positive PCR and/or antibody test, as well as their household contacts (referred to as family members), were invited to three follow-up appointments. The follow-ups were carried out at the earliest possible timepoint within days of screening, then at three and six months after screening at the C19.CHILD Study Clinic. Here, an extended questionnaire including a detailed history of infection was completed, and nasopharyngeal swabs and venous blood samples were collected from all family members willing to participate for SARS-CoV-2 viral RNA and antibody testing.

Sample Processing and Viral RNA Detection

Viral RNA was extracted from nasopharyngeal swabs using a Tecan Freedom Evo liquid handler system (Tecan) and the NucleoSpin 96 Virus Core Kit (Macherey–Nagel; refer to Supplementary Methods for details). For the detection of the SARS-CoV-2 RNA, the RealStar SARS-CoV-2 RT-PCR Kit 1.0 (Altona Diagnostics) was used according to the manufacturer’s recommendations. The dual target assay detects the viral E-gene (B-βCoV-specific) and S-gene (SARS-CoV-2-specific). Samples with positivity in both gene targets were considered positive. SARS-CoV-2 RNA detection of the follow-up participants was performed using the ECDC recommended E-gene assay [10] adapted for high-throughput PCR (Cobas 6800, Roche), as described by S. Pfefferle et al. [11].

Antibody Measurements

SARS-CoV-2-specific antibodies (IgA/IgM/IgG) against the viral nucleocapsid protein were detected in sample serum using the Elecsys® Anti-SARS-CoV-2 Ig assay (Roche) on the cobas c411 system (Roche). Positive results were confirmed in the same serum sample with the LIAISON® SARS-CoV-2 IgG serology test (DiaSorin). This alternative
Statistical Analysis

Frequency of demographic and clinical features was reported for study subjects stratified according to SARS-CoV-2 test results or age groups. Age is shown as mean ± standard deviation, and categorical variables as counts and/or percentages. The primary aim was to estimate the prevalence of SARS-CoV-2 in children and the sample size was justified in this respect. Since only one child was acutely infected, this primary question cannot be answered. Therefore, all analyses are secondary and explorative. Accordingly, the P-values are not adjusted for multiplicity and are only reported as descriptive measures. Children from the same family were included in the study. This creates a cluster structure that must be adequately considered in the statistical methodology. We therefore used mixed logistic models with the family as random intercept, where appropriate. Another issue is the low number of events, which can lead to separation problems and thus instable estimates. We addressed this by using penalized models provided in the R package GLMMadaptive. For the longitudinal analysis of serum antibody concentrations, a generalized linear mixed model was used with random effects for individuals nested within families. The tweedie distribution, which is implemented in the R package glmmTMB, was chosen in this model to account for measurements below the detection limit and, additionally, a zero-inflation was allowed to reflect negative test results. The results were robust with respect to the link function, which was verified in sensitivity analyses. Analyses were performed using R software (version 4.0.2) and GraphPad Prism (version 8.4).

Results

We screened 6113 children under 18 years of age in the Free and Hanseatic City of Hamburg, Germany (population 1,845,017 on April 30, 2020) within a defined time period (May 11–June 30, 2020) and included 5908 study participants from 4506 families in the C19.CHILD study. Children were recruited regardless of the presence or absence of any COVID-19 symptoms. The study included 3145 (53%) volunteers recruited through the C19.CHILD Study Clinic at Kinder-UKE (of these 345 participants in other studies) and 2763 (47%) subjects who presented at one of the Hamburg pediatric hospitals for reasons independent of this study (also see Supplementary Methods). In case of a positive PCR and/or antibody test, children were invited for follow-up tests along with all contact persons living in the same household.

One child tested PCR positive for SARS-CoV-2. Two antibody tests were used for this study. For analysis, the Roche nucleocapsid protein total IgA/IgM/IgG test was defined as screening antibody test (available for 4657 participants, 79% of total included) and the Diasorin S1/S2 spike IgG was defined as confirmatory test. A total of 67 children, 1.44% of all tested, had a positive antibody reaction in both antibody tests in the screening. Participants were recalled for a second testing shortly after positive antibody screening, typically within five days (mean 5.31). Recall testing of seropositives in the screening phase was available for 48 children; all tests remained positive as determined by both methods (Supplementary Table S2) and one child who was only positive in one of the two antibody tests during screening (Diasorin) tested seropositive (Diasorin and Roche positive) in the follow-up. Seven children refused repeat blood draws at immediate follow-up; hence, results from the screening antibody test were used for further analyses (Supplementary Table S2).

In this cohort, the seroprevalence of SARS-CoV-2 increased with age; the mean age of seropositive children was 2 years higher than that of seronegative children (10.3 vs. 8.3 years, \( P = 0.001 \), Table 1). We observed a continuous age effect, where seroprevalence increased with an odds ratio of 1.11 per year of age (95% CI 1.03–1.21, \( P = 0.009 \) Supplementary Figure 1) in the cohort of screened children under 18 years. Inclusion of more than one child per family created a cluster structure, which we considered by applying mixed logistic regression models.

Seroprevalence did not show any gender differences in this cohort (Table 1). Children and adolescents recruited in the participating hospitals often suffered from a complex chronic disease (29% indicated an underlying medical condition, detailed in Supplementary Table S1). One might expect a high proportion of vulnerable individuals in the C19.CHILD study population regarding infection rates or severity of disease [13]. However, children with an underlying medical condition representing almost one-third of the study cohort did not show a difference in the seroprevalence (Table 1, Supplementary Table S1). When comparing self-reported, age-appropriate vaccinations with seroprevalence, children with a complete vaccination status were slightly more likely to be seropositive than children with missed vaccinations (Table 1, 98.5 vs. 92.3%, \( P = 0.060 \)). Participants and their guardians...
were asked to report on any persistent symptoms associated with COVID-19 in the last 14 days before screening. Notably, the only symptom that was more common in seropositive children was loss of taste (seronegatives 15/4590, 1.3%, seropositives 3/67, 21.4%, \( P = 0.001 \)).

We further looked at the effect of self-reported exposure to persons with confirmed SARS-CoV-2 infection on seroprevalence. Exposure was reported for 119 children from whom antibody tests were also available. Twenty-seven of these children had a confirmed positive screening antibody test (22.7%) and 20 were available for recall testing, all of whom tested positive for both nucleocapsid IgA/IgG/IgM and spike IgG. There was no statistically significant difference of seroprevalence for children aged 12–<18 years (seroprevalence 48.1%, OR 3.2, 95% CI 0.5–18.9) as well children aged 6–<12 years (seroprevalence 11.1%, OR 1) after contact to SARS-CoV-2. Furthermore, seroprevalence was higher if the contact had been within the family (92.6% of seropositives after contact, OR 20.9, 95%, CI 3.0–143.8), than if contacts had been outside the family (7.4% of seropositives after contact, OR 1, Table 2).

Next, seroprevalence among household contacts was analyzed. We recalled 45 families for an initial follow-up visit within days after screening (median 83 days post-symptom onset, range 21–121 days based on available data from 39 families). Seroprevalence within single families was 100% only in a minority of cases (Fig. 1A, Supplementary Table S2), where seropositivity was again defined based on a positive result for both nucleocapsid IgA/IgG/IgM and spike IgG. Thirty-eight families were able to identify the first infected person in the household (index case) based on the beginning of symptoms or a known contact to an infected person. Notably, when comparing seroprevalence between individual families, we found that they were lower when the index case was younger than 18 years than for adult index cases (mean seroprevalence 48.9 vs. 73.8%, Fig. 1B). Applying logistic regression to model seroprevalence with the type of index case as predictor confirmed these findings (OR 1.79, 95% CI 1.01–3.19, \( P = 0.047 \)).

The follow-up phase of this study included further recall appointments for the 45 recall families, at 3 months and 6 months after screening (median 173 days, range 112–243 days, and median 254 days, range 193–279 days, post-symptom onset, PSO). Here, PCR and serologic tests were repeated for family members. Twelve families have been lost to follow-up by the end of the study, and in some cases, not all family members were present at every appointment. Six families were excluded from analysis on account of no data available on the date of symptom onset. Despite a steep rise in incidence in Hamburg, Germany, in November–December 2020, no acute infection could be detected in any of the study participants by PCR during follow up.

Longitudinal analysis of antibodies showed that almost all children and adults who were seropositive at the time of the first follow-up retained detectable SARS-CoV-2 antibodies at the time of the third follow up 6 months later (> 193 days after symptom onset). This was observed

| Table 1: Baseline characteristics of the study population. Age is given as mean (standard deviation); all other are counts (percent) or counts/N (percent) in case of missing data. Age is compared using Student’s t-test; all binary data is compared using Fisher’s exact test |
| --- |
| | Negative in either test (\( N=4590 \)) | Positive Roche & DiaSorin (\( N=67 \)) | Total (\( N=4657 \)) | \( p \)-value |
| Age (years) | 8.3 (5.0) | 10.3 (4.4) | 8.3 (5.0) | 0.001 |
| Female gender | 2172 (47.3%) | 33 (49.3%) | 2205 (47.3%) | 0.806 |
| Underlying medical conditions | 1334 (29.1%) | 16 (23.9%) | 1350 (29.0%) | 0.416 |
| Age-appropriate vaccination complete | 4088/4428 (92.3%) | 65/66 (98.5%) | 4153/4494 (92.4%) | 0.060 |
| Contact to persons with known SARS-CoV-2 Infection | 92/1712 (5.4%) | 27/33 (81.8%) | 119/1745 (6.8%) | < 0.001 |

| Table 2: Impact of age and type of contact to a person infected with SARS-CoV-2 on seroprevalence. Odds ratios are estimates from a multiple mixed logistic model |
| --- |
| | Negative in either test (\( N=92 \)) | Positive Roche & DiaSorin (\( N=27 \)) | Total (\( N=119 \)) | Odds ratio (95% CI) |
| Age (grouped) | | | | |
| 0 to < 6 | 21 (22.8%) | 3 (11.1%) | 24 (20.2%) | 1 (reference) |
| 6 to < 12 | 42 (45.7%) | 11 (40.7%) | 53 (44.5%) | 1.1 (0.2, 5.6) |
| 12 to < 18 | 29 (31.5%) | 13 (48.1%) | 42 (35.3%) | 3.2 (0.5, 18.9) |
| Type of contact | | | | |
| Outside family | 60 (65.2%) | 2 (7.4%) | 62 (52.1%) | 1 (reference) |
| Inside family | 32 (34.8%) | 25 (92.6%) | 57 (47.9%) | 20.9 (3.0, 143.8) |
for both types of antibodies measured in this study, with nucleocapsid IgA/IgG/IgM seropositivity retained in 100% of adults \((n=36)\), and 97.6% of children \((n=41)\) and spike IgG seropositivity retained in 94.4% of adults \((n=36)\), and 100% of children \((n=41)\) at six months after screening in those initially positive in both tests.

The spike IgG test allowed for quantitative assessment of serum antibody concentrations. To follow changes in antibody levels of anti-spike IgG over time, statistical modeling using the zero-inflated tweedie-mixed model was applied (Fig. 2). Time points at 90 days, 180 days, and 270 days PSO were chosen for comparison between adults and children, matching the observed time frame in the study cohort (Fig. 2). At all of these time points, children had a higher antibody concentration than adult family members (ratio children vs. adults 90 days PSO 1.75, 95% CI 1.40–2.20, \(P<0.001\); 180 days PSO 1.38, 95% CI 1.08–1.75, \(P=0.01\); 270 days PSO 1.54, 95% CI 1.19–1.99, \(P=0.001\)). During the observed time period, both children and adults had decreasing antibody concentrations over time. For children, the decrease was faster and more pronounced initially (Fig. 2).

### Discussion

Here, we report the results of the C19.CHILD study, a large prospective seroprevalence study for SARS-CoV-2 targeting children in a low-incidence setting. Previous seroprevalence studies carried out under lockdown have compared seroprevalence between children and adults, and found these to be lower in children [14–16]. These findings must be interpreted with caution because different contact patterns of children under lockdown may play a substantial role. A large, population-based seroepidemiological study out of Wuhan, China, a place of high initial incidence, described similar seroprevalence in children and older age groups [17]. In our cohort, seroprevalence among children increased with age, as had been the case for other cohorts of the ancestral SARS-CoV-2, including a seroprevalence study in a similar time interval from the south of Germany [14, 15, 18–20]. These findings may have been specific to the ancestral variant of SARS-CoV-2 and the circumstances governing the early 2020 first wave of coronavirus infections including few imported cases followed by lockdown. Subsequent infection waves, including novel viral variants, showed an increase in seropositivity in children [21].
probably based on the reopening of schools and daycare. At the same time, comparison of seroprevalence in children to adults and older teenagers became less meaningful with the spread of vaccination [21].

We have found that in the case of exposure to a confirmed case of SARS-CoV-2 infection, younger children (zero to under six years) had a lower seroprevalence than older children, although the results did not reach statistical significance. Consistently, lower secondary attack rates have been reported in children than in adults [22–24]. A large study on SARS-CoV-2 transmission dynamics in two Indian states, which included children, provided evidence that contacts between people of similar age are more likely to lead to infection [25]. Thus, a lack of contact between children and their similar-age peers in a lockdown scenario might explain the differences between our data and studies in similar low-incidence settings [15, 16] compared to seroprevalence studies in places with high initial incidence [17].

We report that seroprevalence within individual families with index persons below the age of eighteen years were considerably lower. In our cohort, we made use of the relatively high availability of data on the index person in each family, as in the early phase of the pandemic the source of infection could still be identified in most cases. Most contact tracing and household cluster studies of SARS-CoV-2 have suggested a lower risk of transmission by children [25–30]. In a large population-based cohort study spanning the whole of 2020, older children had a lower risk of transmitting SARS-CoV-2 than younger children, but a comparison with adults was not described [31]. Again, these differences may relate to the highly different contact patterns of children under a general lockdown. In Hamburg, Germany, general school and daycare closure lasted from March 1 to at least May 18, 2020, and recruitment to the C19.CHILD Study began on May 11, shortly before lockdown was lifted. In this period, contacts for children outside their own families were very limited and incidence of novel SARS-CoV-2 infections was low (Supplementary Figure S2). Infection of most index persons in the C19.CHILD cohort probably happened before the lockdown, which is supported by patient histories regarding symptomatic illness in late February and early March (Supplementary Table S2). Subsequently, spread of infection would mostly have been limited to family clusters. As awareness of COVID-19 was high in the public, it may be assumed that symptomatic children, especially teenagers, would have been isolated at home (to the extent possible). The isolation of adult caregivers, however, may have been more difficult. As a result, less transmission would have occurred from children than adults. Alternatively, a less efficient biological transmission of the virus by children in the lockdown setting could explain our findings. As viral loads in nasopharyngeal swabs appear to be similar in children and adults [32, 33], differences in respiratory droplet and aerosol formation [34], respiratory anatomy [35], or increased tropism of the virus in the upper vs. lower airways in children [36, 37] could contribute to the suggested differences in virus transmission. It should be noted that transmission dynamics may be different for more recent variants of SARS-CoV-2. For the B.1.617. (delta) variant, viral loads appeared to be higher than...
for the B.1.1.7 (alpha) variant [38], and significantly increased with age [39]. Research on the delta variant [40] and preliminary reports on the omicron variant [41, 42] indicate their increased airway replication fitness compared to the ancestral and alpha variants, and this could also significantly influence the infectiousness of children with COVID-19.

In our cohort, we provide a longitudinal follow-up of SARS-CoV-2 serology over 9 months after symptomatic illness, showing that children as well as adults retain both anti-spike IgG and anti-nucleocapsid IgA/IgG/IgM antibodies up to 270 days post-symptom onset (PSO). Despite the time elapsed since the beginning of the pandemic, long-term follow-up of quantitative serum antibody measurements such as ours for the ancestral SARS-CoV-2 are scarce in adults and even less has been reported for children. A follow-up of antibodies against SARS-CoV-2 in people living in Wuhan [17], as well as in Jiangsu [43], China, showed antibodies to persist in a majority of cases over six months. However, the authors did not provide data according to time since symptom onset or the age of the participants. Previously, persistence of antibodies in children based on two serological tests 62 days apart was reported, but time since symptom onset was also unknown [44]. One study in a somewhat comparable pediatric cohort showed also detectable IgG levels after 6 months and also in a single child 9 months after infection [45]; however, the cohort did not include adult contacts for comparison. A detailed immunological follow-up of adults [46] after SARS-CoV-2 infection showed similar results 6 to 8 months PSO. Compared to adult family members, children in our cohort showed on average higher anti-spike IgG antibody levels in early convalescence (less than 121 days PSO). A recent work [47] including children aged 3–11 years similarly showed higher antibody levels in children compared to adults against multiple epitopes of SARS-CoV-2, as well as persistent anti-spike antibodies in 14 out of 16 children tested at least 12 months after seroconversion. These findings as well as ours are in contrast to some earlier reports showing lower neutralizing activity [48] or similar anti-spike IgG levels [49] compared to adults, albeit addressed in older pediatric subcohorts. Pre-existing memory B cells and natural antibodies [50] or T cell memory [51, 52] in children on account of more frequent common-cold coronavirus infections may lead to quicker and more efficient SARS-CoV-2-specific immune response and thus higher initial antibody concentrations. The same mechanisms might also contribute to the milder clinical course of SARS-CoV-2 that is characteristic in children. Moreover, as demonstrated in our cohort, anti-spike IgG levels remained higher in children than adults over 193 days PSO, even though a more rapid decline in serum antibody concentrations of children was observed initially.

There are limitations to this study. Teenagers were relatively underrepresented when compared to younger children and Hamburg census data. The retrospective nature of serological testing in this study did not allow for confirmation of infection by direct virus detection (PCR); therefore, seropositivity is used as a surrogate marker for past infection. Furthermore, PCR test results from study participants from the time of infection were not available and index cases in family clusters were identified based on patient history of symptomatic illness (Supplementary Table S2). A selection bias needs to be considered when interpreting our findings. First, our study included over 50% volunteers; second, blood draws were more likely to have been carried out in older children (age distribution of children with available serology compared to the whole study population in Supplementary Figure S3). In this study, no serum neutralization tests have been performed. Instead, seropositivity was defined based on two different serum antibody tests, both of which have shown good correlation with plaque reduction neutralization tests [53, 54]. While this approach does not measure direct antibody-mediated protective immunity, it reduces the probability of false positive tests, especially when multiple family members are assessed. Since the samples used for antibody measurements in this study were obtained after the first 2020 wave of infections, they represent infections with the ancestral SARS-CoV-2 which has now been replaced by more recent viral variants. In spite of this, our data is relevant to antibody responses after vaccination, because all current vaccines are based on inactivated virus or sequences from the ancestral SARS-CoV-2 [55–58]. The setting in which our data was obtained is unique because widespread vaccination and possible repeat infections would complicate designing similar prospective studies in the present day.

In this work, we demonstrated a less than 100% seroprevalence within families in case of infection with the SARS-CoV-2 ancestral variant. Furthermore, seroprevalence within households was lower in case of pediatric than adult index cases. Our findings showing a sustained long-term antibody response in the pediatric population after the initial infection wave of SARS-CoV-2 is relevant for vaccination efforts targeting children as well as newly emerging viral variants.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10875-022-01355-w.

Acknowledgements The C19.CHILD Study Group

Stefanie Ettzold 1, Ingrid Goebel 1, Armin Günther 1, Pia-Sophie Kantor 1, Lea Bandelier 1, Markus Baumanns 1, Pia Dähler 1, Barbara Dwenger 1, Annika Erdmann 1, Sophia Hegselmann 1, Kai Hornig 1, Johanna Jipp 1, Pia Kikkerup 1, Michael Krumm 1, Pelin Kurnaz, M.D. 1, Sabine Pasterkamp 1, Anna Serve 1, Daniel Tegtmeyer, M.D. 1, Julia Terstegen 1, Ceri Theresa Wiedling 1, M.D., Madelaine Wingarth 1, Stefan Rutkowski, M.D. 1, Beate Winkler, M.D. 1, Florian Arndt, M.D. 1, Stefan Blankenberg, M.D. 1, M.D. 3, Daniel Diaz, M.D. 4, Peer Hauck, M.D. 4, Rainer G. Kozluk-Feldmann, M.D. 4, Götz C. Müller, M.D. 4, Veronika C. Stark, M.D. 4, Peter Wieand 1, Martin Aepfelbacher, M.D. 5, Kathrin Cermann 5, Armin Hoffmann, M.D. 5, Johannes K.-M. Knobeloch, M.D. 5, Marylyn M. Addo, M.D. 5, Petra Arck, M.D. 5, Anke Diemert, M.D. 5, Corinna Cramer, M.D. 5, Kurt Hecher, M.D. 5,
Author Affiliations (continued from Title Page)

University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20251 Hamburg, Germany
13 Department of Pediatric Stem Cell Transplantation
14 Department of Pediatric Surgery
15 Neonatology and Intensive Care Unit
16 Department of Pediatric Hematology and Oncology, Research Institute Children’s Cancer Center
17 University Heart and Vascular Center, Epidemiologic Study Center
18 Infectious Diseases Unit, I. Department of Medicine
19 Institute of Human Genetics
20 Helios Mariahilf Klinik, Stader Straße 203 c, 21075 Hamburg, Germany
21 Institute of Virology, Charité Universitätsmedizin Berlin, Charité-platz 1, 10117 Berlin, Germany

Author Contribution GAD, TSM, ACM, and SWG conceived the study. TSM, ACM, and SWG were responsible for study supervision. GAD, MB, MW, MKD, G Engels, KP, PF, KH, FSN, FH, LH, CK, MJK, AK, J Olfe, DEZ, ML, J Oh, TSM, ACM, and SWG contributed to the study design. GAD, MB, MW, MKD, G Engels, KH, FSN, KP, FH, LJH, LH, T Kehl, CK, MJK, AK, J Olfe, F Schlenker, JS, ST, J Oh, TSM, ACM, and SWG coordinated the study and acquired screening data. GAD, MW, G Engels, G Escherich, KH, MKD, KP, JB, LG, FH, LH, T Kehl, CK, MJK, RK, AK, J Olfe, F Schlenker, JS, PS, DEZ, J Oh, TSM, and ACM were responsible for recruitment. Sample preparation was supervised by GAD, MB, G Engels, KP, JB, LJH, F Sibbertsen, and LG; and GAD, MB, LJH, JS, DN, ML, and SWG were responsible for the overview of the laboratory tests. GAD, MB, MW, EV, and AZ performed statistical analysis. All authors provided conceptual input; GAD, MB, MW, ACM, and SWG wrote the essential sections of the manuscript, which was critically revised by all authors.

Funding Open Access funding enabled and organized by Projekt DEAL. The C19 CHILD Hamburg Study received funding from the Senate Chancellery of the Free and Hanseatic City of Hamburg. The following foundations and organizations have provided financial support: Carlsen Verlag, Dr. Melita Berkemann Stiftung, Fördergemeinschaft Kinderkranken- Zentrum Hamburg e.V., Freunde der Kinderklinik des UK Eppendorf e.V., HSV Fussball AG, Joachim-Herz-Stiftung, Michael Otto Stiftung, Michael Stich Stiftung, Nutricia, Stiftung KinderHerz, EAGLES Charity Golf Club e.V., DAMP Stiftung, Krocshke Stiftung, ZEIT-Stiftung.

Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local ethical committee of Hamburg (Ethik-Kommission der Ärztekammer Hamburg, reference number: PV7336).

Consent to Participate Written informed consent was obtained from the parents or legal guardians.

Consent for Publication The authors affirm that parents or legal guardians provided informed consent for publication.

Competing Interests The authors declare no competing interests.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Johns Hopkins University. COVID-19 dashboard by the center for systems science and engineering (CSSE). [cited 18 Jan 2022]. Available: https://coronavirus.jhu.edu/map.html.
2. Tagarro A, Eupalza C, Santos M, Sanz-Santauefemia FJ, Otheo E, Moraleda C, et al. Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid, Spain. JAMA Pediatrics. Am Med Assoc. 2020. https://doi.org/10.1001/jamapediatrics.2020.1346.
3. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatrics. 2020; e20200702. https://doi.org/10.1542/peds.2020-0702.
4. Götzinger F, Santiago-García B, Noguea-Julián A, Lanasa M, Lancellia L, Caló Carducci F, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Heal. 2020;4:653–61. https://doi.org/10.1016/S2352-4642(20)30177-2.
5. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Thecharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet (London, England). 2020. https://doi.org/10.1016/S0140-6736(20)31094-1.
6. Kaushik S, Aydin SI, Derespinia KR, Bansal PB, Kowalsky S, Trachtman R, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2 infection (MIS-C): a multi-institutional study from New York City. J Pediatr. 2020;224:24–9. https://doi.org/10.1016/j.jpeds.2020.06.045.
7. Walter EB, Talata KR, Sabharwal C, Gurtman A, Lockhart S, Paulsen GC, et al. Evaluation of the BNT162b2 Covid-19 vaccine in children 5 to 11 years of age. N Engl J Med. 2022;386:35–46. https://doi.org/10.1056/nejmoa2116298.
8. Wilhelm A, Widera M, Griekscheit K, Toptan T, Schenk B, Pallas C, et al. Reduced neutralization of SARS-CoV-2 Omicron variant by vaccine Sera and monoclonal antibodies. medRxiv. 2021. https://doi.org/10.1101/2021.12.07.21267432

9. CDC Covid-Net. A weekly summary of U.S. COVID-19 hospitalization data; laboratory-confirmed COVID-19-associated hospitalizations. [cited 22 Jan 2022]. Available: https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html

10. Corman VM, Landt O, Kaiser M, Molenkamp R, Mejier A, Chu DK, Detection of, et al. novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. 2019;2020:25. https://doi.org/10.2807/1560-7917.ES.2020.25.3.2000045.

11. Pfefferle S, Reucher S, Nörz D, Lüitgehetmann M. Evaluation of a quantitative RT-PCR assay for the detection of the emerging coronavirus SARS-CoV-2 using a high throughput system. Euro-surveillance. 2020;25:1–5. https://doi.org/10.2807/1560-7917.ES.2020.25.9.2000152.

12. Centers for Disease Control and Prevention. Interim guidelines for COVID-19 antibody testing. 2020.

13. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020. https://doi.org/10.1016/S0140-6736(20)30566-3.

14. Hallal PC, Hartwig FP, Horta BL, Silveira MF, Struchiner CJ, Vidalatti LP, et al. SARS-CoV-2 antibody prevalence in Brazil: results from two successive nationwide serological household surveys. Lancet Glob Heal. 2020;8:e1390–8. https://doi.org/10.1016/S2214-109X(20)30387-9.

15. Stringhini S, Wissnaiak G, Piumatti G, Azman AS, Lauer SA, Bays-S2214-00238-5.

16. Pollán M, Pérez-Gómez B, Pastor-Barriuso R, Oteo J, Hernán MA, Pérez-Olmeda M, et al. Prevalence of SARS-CoV-2 in Spain (EN-COVID): a nationwide, population-based seroepidemiological study. Lancet. 2020;396:535–44. https://doi.org/10.1016/S0140-6736(20)31483-5.

17. He Z, Ren L, Yang J, Guo L, Feng L, Ma C, et al. Seroprevalence and humoral immune durability of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. Lancet. 2020;396:313–9. https://doi.org/10.1016/S0140-6736(20)31304-0.

18. Reicher S, Ratzon R, Ben-Sahar S, Hermoni-Alon S, Mossinon S, Shenhar Y, et al. Nationwide seroprevalence of antibodies against SARS-CoV-2 in Israel. Eur J Epidemiol. 2021. https://doi.org/10.1007/s10654-021-00749-1.

19. Tönshoff B, Müller B, Elling R, Renk H, Meissner P, Hengel H, et al. Prevalence of SARS-CoV-2 infection in children and their parents in Southwest Germany. JAMA Pediatr. 2021. https://doi.org/10.1001/jamapediatrics.2021.0001.

20. Viner RM, Myton OT, Bonell C, Melendez-Torres GJ, Ward J, Hudson L, et al. Susceptibility to SARS-CoV-2 infection among children and adolescents compared with adults: a systematic review and meta-analysis. JAMA Pediatrics. Am Med Assoc. 2020. https://doi.org/10.1001/jamapediatrics.2020.4573.

21. Ooser C, Whitaker H, Linley E, Borrow R, Tonge S, Brown CS, et al. Large increases in SARS-CoV-2 seropositivity in children in England: effects of the delta wave and vaccination. J Infect. 2021;19:21. https://doi.org/10.1016/j.jinf.2021.11.019

22. Yung CF, Kam K qian, Chong CY, Nadua KD, Li J, Tan NWH, et al. Household transmission of severe acute respiratory syndrome coronavirus 2 from adults to children. J Pediatr. 2020;225:249–251. https://doi.org/10.1016/j.jpeds.2020.07.009

23. Madewell ZJ, Yang Y, Longini IM, Halloran ME, Dean NE. Household transmission of SARS-CoV-2: a systematic review and meta-analysis. JAMA Netw open. 2020;3:e2031756. https://doi.org/10.1001/jamanetworkopen.2020.31756.

24. Fung HF, Martínez L, Alarid-Escudero F, Salomon JA, Studdert DM, Andrews JR, et al. The household secondary attack rate of severe acute respiratory syndrome coronavirus 2 (sars-cov-2): a rapid review. Clin Infect Dis. 2021;73:S138–45. https://doi.org/10.1093/cid/ciaa1558.

25. Laxminarayan R, Wahl B, Dudala SR, Gopal K, Mohan C, Neelima S, et al. Epidemiology and transmission dynamics of COVID-19 in two Indian states. Science (80- ). 2020.eaay7672. https://doi.org/10.1126/science.abc7672.

26. Merckx J, Labrecque JA, Kaufman JS. Transmission of SARS-CoV-2 by children. Dtsch Arztebl Int. 2020;117:553–60.

27. Yi S, Kim YM, Choe YJ, Ahn S, Han S, Park YJ. Geospatial analysis of age-specific SARS-CoV-2 transmission patterns in households, Korea. J Korean Med Sci. 2021;36:1–3. https://doi.org/10.3346/jkms.2021.36.e63.

28. Grijaulva CG, Rolffes MA, Zhu Y, Mclean HQ, Hanson KE, Belongia ; Edward A, et al. Transmission of SARS-COV-2 Infections in Households — Tennessee and Wisconsin, April—September 2020. MMWR Mortal Mortal Wkly Rep 2020;69:1631–1634. https://doi.org/10.15585/mmwr.mm944e1

29. Soriano-Arandes A, Gatell A, Serrano P, Biosca M, Campillo F, Capdevila R, et al. Household severe acute respiratory syndrome coronavirus 2 transmission and children: a network prospective study. Clin Infect Dis. 2021;73:e1261–9. https://doi.org/10.1093/cid/ciaa228.

30. Brandal LT, Otftiserova TS, Meijerink H, Rykkvin R, Lund HM, Hungnes O, et al. Minimal transmission of SARS-CoV-2 from paediatric COVID-19 cases in primary schools, Norway, August to November 2020. Eurosurveillance. 2020;26:3–8. https://doi.org/10.2807/1560-7917.ES.2020.26.1.2002011.

31. Paul LA, Daneman N, Schwartz KL, Science M, Brown KA, Whelan M, et al. Association of age and pediatric household transmission of SARS-CoV-2 infection. JAMA Pediatr. 2021;175:1151–8. https://doi.org/10.1001/jamapediatrics.2021.2770.

32. Jones TC, Biele G, Mühlemann B, Veith T, Schneider J, Beheim-Schwarzback J, et al. Estimating infectiousness throughout SARS-CoV-2 infection course. Science (80- ). 2021;373. https://doi.org/10.1126/science.abi2723.

33. Baggio S, L'huillier AG, Verly S, Bellon M, Wagner N, Rohr M, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load in the upper respiratory tract of children and adults with early acute coronavirus disease 2019 (COVID-19). Clin Infect Dis. 2021;73:148–50. https://doi.org/10.1093/cid/ciaa1157.

34. Yang S, Lee GW, Chen CM, Wu CC, Yu KP. The size and concentration of droplets generated by coughing in human subjects. J Aerosol Med Depos Clear Eff Lung. 2007;20:484–94. https://doi.org/10.1089/jam.2007.0610.

35. Wald ER, Schmit KM, Guszland DY. A pediatric infectious disease perspective on COVID-19. Clin Infect Dis. 2020. https://doi.org/10.1093/cid/ciaa1095.

36. Saheb Sharif-Askari N, Saheb Sharif-Askari F, Alabed M, Temsah MH, Al Heialy S, Hamid Q, et al. Airways expression of SARS-CoV-2 receptor, ACE2, and TMPRSS2 is lower in children than adults and increases with smoking and COPD. Mol Ther - Methods Clin Dev. 2020;18:1–6. https://doi.org/10.1016/j.omtm.2020.05.013.

37. Muus C, Luecken MD, Ersalan G, Waghray A, Heinberg G, Sikkema L, et al. Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights
inflammatory programs in putative target cells. bioRxiv. 2020;2020.04.19.049254. https://doi.org/10.1101/2020.04.19.049254

38. Costa R, Olea B, Bracho MA, Albert E, de Michelen P, Martinez-Costa C, et al. RNA viral loads of SARS-CoV-2 Alpha and Delta variants in nasopharyngeal specimens at diagnosis stratified by age, clinical presentation and vaccination status. J Infect. 2021;29–31. https://doi.org/10.1016/j.jinf.2021.12.018

39. Singanayagam A, Hakki S, Dunning J, Madon KJ, Crane MA, Koycheva A, et al. Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study. Lancet Infect Dis. 2021;3099. https://doi.org/10.1016/S1473-3099(21)00648-4

40. Mlochova P, Kemp S, Dhar MS, Papa G, Meng B, Ferreira IATM, et al. SARS-CoV-2 B.1.617.2 Delta variant replication and immune evasion. Nature. 2021;599. https://doi.org/10.1038/s41586-021-03944-y

41. Chan MCW, Hui KPY, Ho J, Cheung M, Ng K, Ching R, et al. SARS-CoV-2 Omicron variant replication in human respiratory tract ex vivo. Nat Portf. 2022. https://doi.org/10.21203/rs.3.rs-1189219/v1

42. Peacock TP, Brown JC, Zhou J, Thakur N, Newman J, Kugathasan R, et al. The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry, bioRxiv. 2022;2022.12.31.474653. https://doi.org/10.1101/2021.12.31.474653

43. Zhu L, Xu X, Zhu B, Guo X, Xu K, Song C, et al. Kinetics of SARS-CoV-2 specific and neutralizing antibodies over seven months after symptom onset in COVID-19 patients. Microbiol Syst. 2021;9. https://doi.org/10.1128/spectrum.00590-21

44. Roarty C, Trony C, McFetridge L, Mitchell H, Watson C, Waterfield T, et al. Kinetics and seroprevalence of SARS-CoV-2 antibodies in children. Lancet Infect Dis. Lancet Publishing Group; 2020. https://doi.org/10.1016/S1473-3099(20)30884-7

45. Oygur PD, Ozsurekci Y, Gurlevik SL, Aykac K, Kuluk MG, Cura Yayla BC, et al. Longitudinal follow-up of antibody responses in pediatric patients with COVID-19 up to 9 months after infection. Pediatr Infect Dis J. 2021;40:E294–9. https://doi.org/10.1097/INF.000000000003199.

46. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science (80- ). 2021;371. https://doi.org/10.1126/science.abc4063

47. Dowell AC, Butler MS, Jinks E, Tut G, Lancaster T, Sylla P, et al. Children develop robust and sustained cross-reactive spike-specific immune responses to SARS-CoV-2 infection. Nat Immunol. 2022;23:40–9. https://doi.org/10.1038/s41590-021-01089-8

48. Pierce CA, Preston-Hurlburt P, Dai Y, Burn Aschner C, Cheshenko N, Galen B, et al. Immune responses to SARS-CoV-2 infection in hospitalized pediatric and adult patients. Sci Transl Med. 2020.

49. Weisberg SP, Connors TJ, Zhu Y, Baldwin MR, Lin W-H, Wontakal S, et al. Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum. Nat Immunol. 2020. https://doi.org/10.1038/s41590-020-00826-9

50. Carsetti R, Quintarelli C, Quinti I, Piano Mortari E, Zumla A, Ippolito G, et al. The immune system of children: the key to understanding SARS-CoV-2 susceptibility? Lancet Child Adolesc Health. Elsevier B.V.; 2020;414–416. https://doi.org/10.1016/S2352-4642(20)30135-8

51. Sette A, Crotty S. Pre-existing immunity to SARS-CoV-2: the knowns and unknowns. Nature Reviews Immunol. Nat Res. 2020;457–458. https://doi.org/10.1038/s41577-020-0389-x

52. Braun J, Loyal L, Frenitsis M, Wendisch D, Georg P, Kurth F, et al. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. Nature. 2020;587:270–4. https://doi.org/10.1038/s41586-020-2598-9

53. Kohmer N, Westhaus S, Ruhl C, Ciesek S, Rabenau HF. Brief clinical evaluation of six high-throughput SARS-CoV-2 IgG antibody assays. J Clin Virol. 2020;129. https://doi.org/10.1016/j.jcv.2020.104480.

54. Bahar B, Jacquot C, Mo YD, DeBiase RL, Campos J, Delaney M. Kinetics of viral clearance and antibody production across age groups in children with severe acute respiratory syndrome coronavirus 2 infection. J Pediatr. 2020;227:31-37.e1. https://doi.org/10.1016/j.jpeds.2020.08.078.

55. Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020;586:589–93. https://doi.org/10.1038/s41586-020-2639-4

56. Corbett KS, Edwards DK, Leist SR, Abiona OM, Boyoglu-Barnum S, Gillespie RA, et al. SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. Nature. 2020;586:567–71. https://doi.org/10.1038/s41586-020-2622-0

57. Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis. 2021;21:39–51. https://doi.org/10.1016/S1473-3099(20)30831-8.

58. Wang H, Zhang Y, Huang B, Deng W, Quan Y, Wang W, et al. Development of an Inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2. Cell. 2020;182:713-721.e9. https://doi.org/10.1016/j.cell.2020.06.008.
Authors and Affiliations

Gabor A. Dunay¹ · Madalena Barroso¹ · Mathias Woidy¹ · Marta K. Danecka¹ · Geraldine Engels¹ · Katharina Hermann² · Friederike S. Neumann¹ · Kevin Paul¹ · Jan Beime² · Gabriele Escherich³ · Kristin Fehse¹ · Lev Grinstein² · Franziska Haniel¹ · Luka J. Haupt¹ · Laura Hecher² · Torben Kehl⁴ · Christoph Kemen⁵ · Markus J. Kemper⁶ · Robin Kobbe⁷ · Aloisa Kohl² · Thomas Klokow¹ · Dominik Nörz⁸ · Jakob Olfe⁴ · Friderike Schlenker² · Jessica Schmiesing¹ · Johanna Schrum³ · Freya Sibbertsen¹ · Philippe Stock⁹ · Stephan Tiede¹ · Eik Vettorazzi¹⁰ · Dimitra E. Zazara²,¹¹ · Antonia Zapf¹⁰ · Marc Lütgehetmann⁸ · Jun Oh² · Thomas S. Mir⁴ · Ania C. Muntau² · Søren W. Gersting¹ · the C19.CHILD Study Group

¹ University Children’s Research, UCR@Kinder-UKE, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20251 Hamburg, Germany
² Department of Pediatrics, Kinder-UKE, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20251 Hamburg, Germany
³ Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20251 Hamburg, Germany
⁴ Department of Pediatric Cardiology, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20251 Hamburg, Germany
⁵ Wilhelmstift Children’s Hospital, Liliencronstraße 130, 22149 Hamburg, Germany
⁶ Asklepios Klinik Nord – Heidelberg, Tangstedter Landstraße 400, 22417 Hamburg, Germany
⁷ Institute for Infection Research and Vaccine Development (IIRVD), University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20251 Hamburg, Germany
⁸ Institute of Medical Microbiology, Virology and Hygiene, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20251 Hamburg, Germany
⁹ Altona Children’s Hospital, Bleickenallee 38, 22763 Hamburg, Germany
¹⁰ Institute of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20251 Hamburg, Germany
¹¹ Department of Obstetrics and Prenatal Medicine, Division for Experimental Feto-Maternal Medicine, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20251 Hamburg, Germany