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Immunocompromised children and young people are at no increased risk of severe COVID-19

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Aims: We aimed to prospectively describe the incidence and clinical spectrum of SARS-CoV-2 infection in immunocompromised paediatric patients in the UK.

Methods: From March 2020 to 2021 weekly questionnaires were sent to immunocompromised paediatric patients or their parents. Information, including symptom presentation and SARS-CoV-2 PCR test results, was collected from 1527 participants from 46 hospitals. Cross-sectional serology was investigated in February and March 2021.

Results: Until the end of September 2020, no cases were reported. From September 28th 2020 to March 2021 a total of 38 PCR-detected SARS-CoV-2 infections were reported. Of these, four children were admitted to hospital but none had acute severe COVID-19. Increasing age in association with immunodeficiency increased reporting of SARS-CoV-2 infection. Worsening of fever, cough, and sore throat were associated with participants reporting SARS-CoV-2 infection. Serology data included 452 unvaccinated participants. In those reporting prior positive SARS-CoV-2 PCR, there were detectable antibodies in 9 of 18 (50%). In those with no prior report of infection, antibodies were detected in 32 of 434 (7.4%).

Conclusions: This study shows SARS-CoV-2 infections have occurred in immunocompromised children and young people with no increased risk of severe disease. No children died.

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Large multicentre cohort studies from USA, UK, and Europe show low overall numbers of paediatric hospital admissions due to coronavirus disease 2019 (COVID-19) with a low proportion of these being admitted to paediatric intensive care units.\textsuperscript{5,13,14} These cohort studies and national data from USA, UK, Italy, Germany, Spain, France, and South Korea show that COVID-19 mortality risk is low in children and young people.\textsuperscript{15}

Parents, clinicians, and public health bodies globally have remained concerned about risk of SARS-CoV-2 infection to children and young people living with chronic health conditions. In the absence of paediatric data, many immunocompromised children and young people in the UK were initially deemed "extremely vulnerable" to the effects of SARS-CoV-2 infection. Against the advice of many specialist clinicians and NICE,\textsuperscript{16} many individuals were advised to adopt specific precautionary "shielding" measures, were subject to school closures, and have had reduced access to healthcare, causing significant burden on both them and their families.\textsuperscript{17,18}

Evidence on the risks of SARS-CoV-2 in immunocompromised paediatric patients is beginning to emerge. A large systematic review with meta-analysis and a large retrospective cross-sectional study, found paediatric patients with chronic health conditions were at higher risk of severe COVID-19 compared to those without.\textsuperscript{19,20} However, rates of serious disease (relative risk ratio 1+79 (95% CI 1+27 – 2+51))\textsuperscript{18} were very small in proportion to other causes of morbidity and mortality in children and only 26/9353 children with comorbidities had immune disorders.\textsuperscript{19} To accurately understand and assess the risk in cohorts of immunocompromised paediatric patients, further population and serology studies are required. Currently there are a limited number of studies reporting seroprevalence in immunocompromised paediatric patients\textsuperscript{21–25} although some studies have not yet been reported.\textsuperscript{26,27}

We aimed to prospectively describe the incidence and clinical spectrum of SARS-CoV-2 infection in a UK-wide cohort of immunocompromised children and young people. A secondary aim was to characterise risk factors and predictive symptoms for SARS-CoV-2 infection in this cohort.

Materials and methods

This prospective cohort study was carried out over one year (16th March 2020–14th March 2021) and included immunocompromised children and young people under the age of 19 years. Immunocompromise was defined as having any medical indication for an annual influenza vaccine, in keeping with UK public health guidelines.\textsuperscript{26} Participants were recruited from 46 hospitals across the UK between March and July 2020. Participants and parents received information sheets electronically with a link to an online consent form. They received electronic reminders and were removed from the study database after three weeks in the absence of consent. Participants who had consented to participate in the study were asked to complete an online questionnaire every week, with questions based on the ISARIC and WHO COVID-19 Case Report Form.\textsuperscript{29} Information was collected regarding symptom presentation, test results, health care attendance, hospital admission, and the effects of COVID-19 on daily life. Results from the first four months of the study have been published.\textsuperscript{18}

Participants self-reported when a SARS-CoV-2 PCR test was carried out and found to be positive. These tests were sought according to UK government guidelines with testing capacity increasing through the study period. Initially testing was limited to hospital admissions. From 18th May 2020 those aged over five years with symptoms could seek a test and from 27th May 2020 testing was expanded to those under five years and contact tracing began.\textsuperscript{30,31}

Participants reporting positive PCR swabs were emailed to clarify result and clinical outcomes.

The study gained ethical approval from the Yorkshire and the Humber – Leeds West NHS Research Ethics Committee (IRAS 281544).

Cohort

1645 participants consented to the study. Of these, 1527 successfully completed at least one weekly questionnaire. A further 505 were withdrawn during the study period (Fig. 1). The commonest reason for withdrawal was not completing the survey for three successive weeks. At week 32, the study team started contacting participants who had not completed questionnaires for three successive weeks regarding ongoing participation. This led to a sharp rise in withdrawals. Median age was 11 years (range 0–18). 55•1% of participants were female. Baseline characteristics are displayed in Table 1.

Serology

Between December 2020 and January 2021 all participants (n = 1073) were invited to take part in an optional serology sub-study. They were provided with information sheets electronically with a link to an online consent form. Consenting participants were sent sampling kits via post between February and March 2021. Participants collected a dried blood sample using a safety lancet and Mitra\textsuperscript{®} sampling device. Validated in-house enzyme-linked immunosorbent assays (ELISA) were carried at the virology laboratories of the University of Nottingham to detect SARS-CoV-2 anti-nucleocapsid and anti-spike IgG antibodies, as previously described.\textsuperscript{32} All assays were performed on Operonets OT-2 Precision liquid handling robots (full protocol available on request). Original assay validations were performed on a separate sample set using commercial anti-S1 (Euroimmun) and anti-N assays (Roche) and conducted at the Rare and Imported Pathogens Laboratory at Public Health England using manufacturers’ protocols.

Antibodies were first extracted from dried samples to a 1:15 dilution by shaking for 2 h in 150 μL phosphate buffered saline (PBS) containing 0•1% Triton-x100 and 0•05% sodium azide. Extracted samples were diluted to 1:120 with 3% skimmed milk powder in PBS containing 0•05% Tween 20 and 0•05% sodium azide. ELISAs were performed by coating 384 well NUNC maxisorp plates (Thermofisher) with either 20 μL/well of 0•5 μg/mL of SARS-CoV-2 spike protein S1 subunit (His-tagged; Sinobiologics, GmbH) or SARS-CoV-2 Nucleocapsid (His-Tagged; Sinobiologics, GmbH) in carbonate-bicarbonate buffer (CBC; Merck UK), sealing with foil film and incubating overnight at 4 °C. Wells were then washed three times with 100 μL PBS with 0•05% Tween 20 (PBST) using a Thermofisher Wellwash Versa plate washer with a final aspirate. Wells were immediately filled with 100 μL of 3% skimmed milk powder (w/v) in PBS and 0•05% sodium azide, foil sealed and blocked overnight at 4 °C. Assay plates were then washed three times as before and duplicate wells filled with 20 μL of the 1:120 diluted sample, diluted in 3% skimmed milk powder (w/v) in PBS and 0•05% sodium azide.

Control samples included duplicates of a 1:120 dilution of a pool of sera derived from 32 individuals previously identified as having high nucleocapsid and high spike S1 reactivity. Three negative samples, each derived from a separate pool of 21 pre-covid sera were added to separate wells in duplicate. Wells containing only dilution buffer were used as non-serum blank. After 15 min incubation at room temperature (21 °C), the plate was washed three times in PBST. This was followed by addition to each well of 20 μL of gamma chain-specific anti-human IgG-HRP conjugate (Sigma A0170–1ML) at 1:30,000 dilution in PBST and incubation for 15 min at room temperature. Wells were then washed three
Fig. 1. Weekly participant numbers and weekly questionnaire response rate (16th March 2020–14th March 2021).

Table 1
Characteristics of participants referred to the ImmunoCOVID study.

|                      | Referred but not participating | Withdrewn participants | Currently active participants | COVID positive (subset) |
|----------------------|-------------------------------|------------------------|------------------------------|------------------------|
| Sample size          | 1373                          | 505                    | 1022                         | 38                     |
| Female               | 53•8%                         | 54•5%                  | 55•1%                        | 55•3%                  |
| Teenagers            | 64•4%                         | 55•6%                  | 55%                          | 68•4%                  |
| Age                  | 11•9 + 4•3**                  | 10•8 + 4•1            | 10•7 + 4•1                  | 12•6 + 4•2**           |
| UK geography         |                               |                        |                              |                        |
| South                | 9•9%                          | 16•6%                  | 21•4%                        | 18•4%                  |
| Middle               | 44•0%                         | 41•1%                  | 42•1%                        | 47•4%                  |
| North                | 46•1%                         | 42•3%                  | 36•5%                        | 34•2%                  |
| Treatment team       |                               |                        |                              |                        |
| Rheumatology         | 42•8%                         | 48•2%                  | 48•7%                        | 52•6%                  |
| Immunology           | 8•1%                          | 10•4%                  | 9•3%                         | 13•2%                  |
| Respiratory          | 7•7%                          | 6•3%                   | 5•1%                         | 5•3%                   |
| Oncology             | 5•3%                          | 2•6%                   | 4•3%                         | 7•9%                   |
| Gastroenterology     | 7•5%                          | 8•3%                   | 9•7%                         | 2•6%                   |
| Nephrology           | 11•7%                         | 12%                    | 10•7%                        | 7•9%                   |
| Neurology            | 3•1%                          | 3•9%                   | 2•2%                         | 0%                     |
| Haematology          | 3•7%                          | 1•6%                   | 2•3%                         | 2•6%                   |
| Neonatology          | 0•3%                          | 0•2%                   | 0•2%                         | 0%                     |
| Diabetes             | 7•3%                          | 5•1%                   | 5•3%                         | 5•3%                   |
| Infection            | 2•0%                          | 0•4%                   | 0•4%                         | 2•6%                   |
| Dermatology          | 0•5%                          | 0•8%                   | 0•9%                         | 0%                     |
| Heart and Lung       | 0•1%                          | 0•2%                   | 0•2%                         | 0%                     |
| Diagnosis            |                               |                        |                              |                        |
| Gastroenterology     | 10•7%                         | 13•1%                  | 0•%                          |                        |
| Nephrology           | 11%                           | 9%                     | 10•8%                        |                        |
| Transplants          | 7•4%                          | 7•6%                   | 13•5%                        |                        |
| Diabetes             | 6•4%                          | 6•5%                   | 5•4%                         |                        |
| Immune deficiency    | 10•3%                         | 8•7%                   | 18•9%                        |                        |
| Oncology             | 5•6%                          | 7•7%                   | 10•8%                        |                        |
| Respiratory          | 7•2%                          | 8•5%                   | 8•1%                         |                        |
| Other                | 29•1%                         | 26•7%                  | 29•7%                        |                        |
| Juvenile idiopathic  | 37•4%                         | 35•4%                  | 40•5%                        |                        |
| Arthritis            | 15•5%                         | 18•5%                  | 16•2%                        |                        |
| Other immune condition |                             |                        |                              |                        |
| Medication           |                               |                        |                              |                        |
| Other drugs          | 49%                           | 53•7%                  | 58•8%                        |                        |
| Chemotherapy         | 0•9%                          | 0•8%                   | 0%                           |                        |
| Antibiotics          | 16•5%                         | 16%                    | 16•7%                        |                        |
| Other                | 16•7%                         | 21•6%                  | 23•7%                        |                        |
| immunosuppressants   | 17•5%                         | 19%                    | 16•7%                        |                        |
| Systemic             | 34•7%                         | 35•1%                  | 25%                          |                        |
| corticosteroids      | 27•2%                         | 29•3%                  | 27•8%                        |                        |
| Biologics            |                               |                        |                              |                        |
| Methotrexate         |                               |                        |                              |                        |

Statistical significance is calculated with Chi-Square statistics. If one or more cells in the contingency table had an expected count of less than five the Fisher's exact statistic was calculated. Group differences in age were calculated with F test.

• significant at 0•05 level.
•• significant at 0•01 level.
••• significant at 0•001 level.
times in PBST. 40 μl of One-step ultraTMB substrate solution (Thermo
disher) was added to each well. After 20 min incubation at room
temperature, 40μl of 2 N H2SO4 was added to each well and the
384 well plate read at 450 nm absorption in a GlowMax Explorer
microplate reader (Promega Corp.). Data from absorbance measure-
ments were output to Excel data sheets and subsequently imported
into Graphpad Prism for basic analysis. More detailed statistical
analysis was then carried out on SPSS.

Seropositivity was indicated according to the ratio method (i.e.
ratio of the average sample optical density/average Negative optical
density). According to this approach a ratio of > = 1×1 was classi-
fied as positive and a ratio of < 1×1 was classified as negative.

Statistical analysis

Data cleaning, formatting, and analyses were performed with
SAS 9.4 (SAS Institute INC, Cary NC). Survival analysis techniques
were used to explore the risk of SARS-CoV-2 infection, as mea-
sured by PCR testing, to participants throughout the first year
of the study. The semi-parametric methodology of Cox regres-
sion (Cox, 1972) was employed. Factors associated with the risk
of SARS-CoV-2 infection were determined. In addition, the symp-
toms uniquely experienced at time of SARS-CoV-2 infection were
determined. For analysis purposes we have treated infection as a
non-repeated event. Data was collected on a weekly basis, creat-
ing ties in the data. Parameters are therefore estimated using the
estimation method developed by Efрон (1977). Participant infor-

Role of the funding source

The funders had no role in study design, data collection, data
analysis, data interpretation, or writing of the manuscript. The cor-
responding author had full access to all data and had final respon-
sibility for the decision to submit for publication.

Results

PCR confirmed cases

Participants reported a total of 1355 PCR tests through the study
period. The majority of participants (919, 60.2%) did not re-
port any PCR tests. 576 (37.8%) reported between 1 and 5 tests
and 2% reported between 6 and 20 tests. During the government
advised shielding period (March–August 2020) no SARS-CoV-2 in-
fections were reported. The first positive SARS-CoV-2 PCR test was
in week 30 (28th September–5th October). Further positive tests
were subsequently reported, with peaks in rates in weeks 36 (9th–
15th November 2020) and 42 (21st–27th December 2020) with five
and six cases, respectively [Fig. 2]. There were a total of 38 PCR
detected SARS-CoV-2 infections, giving an incidence rate of 3.7%
(n = 1022). Of these six were asymptomatic, 28 had symptoms
managed at home, and four reported hospital admission. Those re-
porting hospital admissions are described in Table 2. These partic-
ipants all had varying presentations and significant underlying co-
morbidities and therapies; two were transplant patients, one had
acute lymphoblastic leukaemia, and one had X-linked agamma-
globulinemia. Clinical presentation was varied but none reported
acute severe COVID-19 or paediatric multisystem inflammatory
syndrome. None were admitted to paediatric intensive care units
or died.

Hazard analysis

Assuming that hazard remained constant between August 2020
and March 2021, an estimate of hazard across the whole cohort
is 0.00148 or 38/25,687 (number of cases/ total number of an-
swered questionnaires). This is equivalent to a positive SARS-CoV-
2 PCR test once every 676 weeks. This hazard was in the context
of varying disease incidence during the pandemic, and varying ap-
proaches of participants to shielding or not. While NHS electronic
systems sent text messages telling children and young people des-
ignated “at risk” to shield based on adult diagnostic categories and
the assumed risk, many specialist clinicians advised school atten-
dance to children with all but the most severe immune problems.16

The significance of different demographic (sex, age, geograph-
ical region), diagnosis and medication use covariates, as well as
time-dependent symptom covariates were tested. The best multi-

Serology

478 participants provided serology samples and their baseline
characteristics are displayed in Table 4. However, participants in
this cohort were not representative of those overall. Young peo-
ple over ten years, those with “other diagnoses” or diabetes; and
those on “other drugs”, biologics or methotrexate were more likely
to take part in this sub-study. There was also geographical varia-
tion in participation. Rates by vaccination status in all and by sex,
age, and prior PCR status in those unvaccinated are displayed in
Table 5.

26 participants reported receiving a first dose of a COVID vac-
cine prior to serology. Of these, six (23.1%) were serologically po-
itive with a mean of 23 days between vaccination and sampling
(range 14–33). Three of these were positive for only anti-S1 IgG
and three positive for both anti-S1 and anti-N IgG. Those who were
negative had a mean of 15–65 days between vaccination and sam-
ping (range 1–42). Vaccinated participants were excluded from
further analysis.

Of 452 unvaccinated participants, anti-N and/or anti-S antibod-
ies were detected in 41 samples (9.1%). Of those participants re-
porting a prior positive PCR test 18 took part in the serology sub-
study and of these, antibodies were detected in nine (50%). Four
of these were positive for only anti-N IgG, one positive for only
anti-S1 IgG, and four positive for both anti-N and anti-S1 IgG. In
those with no previous positive PCR test, antibodies were detected
in 32 of 434 (7.4%). Seventeen of these were positive for only anti-
N IgG, six positive for only anti-S1 IgG, and nine positive for both
Table 2
Description of PCR positive SARS-CoV-2 infection reporting hospital admission.

| Week of PCR | Week of admission | Age in years | Sex | Admission Details | Past Medical History | Baseline Medication |
|-------------|------------------|--------------|-----|-------------------|----------------------|---------------------|
| 42          | 42               | 17           | Male| Admitted with negative PCR, symptoms of bowel obstruction and underwent laparotomy. Asymptomatically tested positive prior to discharge. Subsequently readmitted with fever and abdominal pain for three days before symptom resolution. Subsequent serology negative. | liver transplant, atypical haemolytic uraemic syndrome, chronic kidney disease, and superior vena cava stenosis | prednisolone, sirolimus, mycophenolate mofetil, hydralazine, doxazosin, amlodipine, losartan, atenolol, allopurinol, and desloratadine |
| 42          | 44               | 12           | Male| Initially tested positive with only symptom being abdominal pain. Subsequently admitted for two days with bacterial chest infection. Put down to post viral immunosuppression. Admission swab negative. Subsequent serology negative. | heart transplant | sirolimus, mycophenolate mofetil, pravastatin, and melatonin |
| 43          | 52               | 17           | Male| Tested positive, initially managed at home with antibiotics. Subsequently had persistent fever leading to investigation with bronchoscopy which showed changes consistent with SARS-CoV-2 infection. Five day admission for remdesivir giving symptom resolution. | X-linked agammaglobulinemia | human normal immunoglobulin |
| 45          | 45               | 6            | Male| Household tested positive two weeks prior but no test sought at time for participant. Admission with anaemia for two days with positive PCR swab. Received one unit of blood. Tests for leukaemia relapse negative. | acute lymphoblastic leukaemia, asthma, and autism | mercaptopurine, co-trimoxazole, gabapentin, fluticasone with salmeterol, montelukast, methotrexate, macrogol, and esomeprazole |

Table 3
Cox hazard estimates for SARS-CoV-2 infection (controlling for other immunosuppressant treatment).

| Covariate                                | Coefficient | Standard error | P-value | Hazard Ratio | 95% confidence interval HR |
|------------------------------------------|-------------|----------------|---------|--------------|---------------------------|
| Age                                      | 0.13        | 0.05           | 0.006   | 1.14         | 1.04–1.25                 |
| Immune deficiency                        | 1.05        | 0.45           | 0.02    | 2.87         | 1.18–6.94                 |
| Worsening of fever in week of infection  | 3.25        | 0.75           | <0.0001 | 25.79        | 5.94–112.01               |
| Worsening of cough in week of infection  | 2.42        | 0.69           | 0.0005  | 11.29        | 2.91–43.73                |
| Worsening of sore throat in week of infection | 2.00       | 0.69           | 0.0037  | 7.41         | 1.02–26.01                |
anti-N and anti-S1 IgG. Associations were tested and are shown in Table 4. Detection of antibodies was associated with being female and over ten years old. Associations were also found with having had a transplant and being on immunosuppressants or corticosteroids. In those with prior positive PCR tests no associations were found between serology result and interval between positive test and serology test.

**Table 4**

| Characteristics of participants participating in serology testing. |
|---------------------------------------------------------------|
| **No serology** | **Serology** | **Positive serology** | **Negative serology** |
| Sample size | 1167 | 478 | 47 | 431 |
| Female | 53.6% | 56.4% | 68.1% | 55.1% |
| Teenagers | 52.7% | 61.0% | 80.9% | 58.8% |
| **UK geography** | | | | |
| Middle North | 18.2% 41.3% 34.3% | 23.0% 41.3% 34.2% | 21.4% 39.6% 17.0% | 22.3% 41.5% 36.1% |
| Age | 10.34 4.5 | 11.34 4.2 | 13.53 3.7 | 11.10 4.1 |
| **Diagnosis** | | | | |
| Gastroenterology | 12.3% 9.9% 7.3% | 12.5% 7.6% 4.8% | 17.0% 12.8% 17.0% | 12.0% 7.0% 6.8% |
| **Medication** | | | | |
| Drugs | 45.2% 0% 15.2% | 56.6% 0% 15.1% | 59.5% 0% 11.4% | 56.3% 1% 15.5% |
| **Sex** | | | | |
| Female | 21.7% 0% 9% | 21.0% 0% 9% | 31.9% 27.3% 43.2% | 19.8% 18.0% 40.7% |
| Male | 24.8% | 32.1% | 22.7% | 33.2% |
| **Total** | | | | |
| Vaccinated | 0 | 7 | 3 | 0 |
| Non-vaccinated | 21 | 10 | 13 | 431 |
| **Age group** | | | | |
| 0–5 years | 15 | 4 | 10 | 223 |
| 6–10 years | 6 | 3 | 3 | 188 |
| 11–15 years | 21 | 7 | 13 | 411 |
| **Prior PCR status** | | | | |
| PCR positive | 3 | 1 | 4 | 9 |
| PCR negative | 17 | 6 | 9 | 402 |

**Table 5**

| Serology rates by vaccination status, sex, age group, and prior PCR status (only unvaccinated in the latter three tables). |
|---------------------------------------------------------------|
| **No vaccine** | **Anti-N IgG positive** | **Anti-S1 IgG positive** | **Both positive** | **Seronegative** | **Totals** | **Total seropositive (%)** |
| Vaccinated | 0 | 3 | 3 | 20 | 452 | 41 (9.1%) |
| Non-vaccinated | 21 | 10 | 13 | 431 | 478 | 47 (9.8%) |
| **Sex** | | | | | | |
| Female | 15 | 4 | 10 | 223 | 252 | 29 (11.5%) |
| Male | 6 | 3 | 3 | 188 | 200 | 12 (6.0%) |
| **Table** | | | | | | |
| **Age group** | | | | | | |
| 0–5 years | 0 | 0 | 0 | 26 | 26 | 0 (0.0%) |
| 6–10 years | 5 | 0 | 2 | 125 | 132 | 7 (5.3%) |
| 11–15 years | 7 | 2 | 5 | 167 | 181 | 14 (7.7%) |
| 16+ years | 9 | 5 | 6 | 93 | 113 | 20 (17.4%) |
| **Prior PCR status** | | | | | | |
| PCR positive | 4 | 1 | 4 | 9 | 18 | 9 (50.0%) |
| PCR negative | 17 | 6 | 9 | 402 | 434 | 32 (7.4%) |
| **Total** | 21 | 7 | 13 | 411 | 452 | 41 (9.1%) |

Discussion

We have demonstrated that this cohort of immunocompromised paediatric patients were at no increased risk of severe COVID-19 during the first two waves of the COVID-19 pandemic in the UK, supporting current NICE guidance. During the government-advised shielding period during the first wave of the pandemic, no participant reported a positive test for SARS-CoV-2, suggesting that shielding measures were effective or testing capacity was insufficient. Subsequently, the peaks in cases in mid-November and late December in our cohort, correspond to peaks in overall UK prevalence and in paediatric prevalence in England during the second wave of the pandemic. The majority of those who did report positive PCR tests were managed at home. The four participants who reported hospital admission had diverse clinical presentations with none reporting admission due to acute severe COVID-19 or paediatric multisystem inflammatory syndrome (Table 2). No clear patterns or risk factors for admission are evident from data on those admitted. The presentations of anaemia in the participant with acute lymphoblastic leukaemia and delayed COVID lung changes in the participant with X-linked agammaglobulinaemia supports ongoing vigilance for atypical COVID presentations in this diverse cohort. The reason participants were not at increased risk of severe disease is unclear. Children in general seem to be less affected and a potential additional factor may be that the participants chronic health conditions or
medications, often immunosuppressive, reduce the risk of the excessive immune response that is a hallmark of severe COVID-19.

Increased hazard of SARS-CoV-2 infection with age is in keeping with overall paediatric rates reported in England and USA.\textsuperscript{2,35} This may represent increased symptom burden with age, as in the general paediatric population a bimodal distribution of severity has been observed with peaks in those under one year and over ten years.\textsuperscript{2,14} It may also represent increased social mixing with age.

While immune deficiency was found to increase hazard of infection, there was no increased risk of admission in this group. This is a novel observation and has not been observed from initial\textsuperscript{36} or more recent data (Dr AM Shields, personal communication, July 2021) from the United Kingdom Primary Immunodeficiency Network. An Italian registry study including 1396 paediatric patients with primary immunodeficiency over one year from February 2020, found a lower incidence of infection (33, 2\%3\%6\%) compared to the general paediatric population.\textsuperscript{37} In a separate cohort, only three of 582 paediatric hospital admissions with SARS-CoV-2 infection had immunodeficiency with none admitted to intensive care.\textsuperscript{14}

Recognising symptoms of COVID-19 is a challenge in this population, due to symptom variability and overlap with those of chronic medical conditions. This study shows that in immunocompromised children, worsening of fever, cough, and sore throat were associated with a positive PCR test in the same week. Symptoms of fever and cough are common with SARS-CoV-2 infection and sore throat has been reported as being more common with the delta variant.\textsuperscript{38}

Serology

While 9\%1\% (41/452) of unvaccinated children and young people tested positive for antibodies reactive to SARS-CoV-2 in the serology sub-study, only 2\%5\% (38/1527) reported positive SARS-CoV-2 PCR during the survey study. This suggests a proportion of participants had infection which was not confirmed by PCR test. Only 50\% (9/18) of participants included in the serology sub-study who reported prior positive SARS-CoV-2 PCR tested positive for antibodies reactive to SARS-CoV-2. Half of PCR positive participants were not serologically positive when tested and some seroconverted with no prior detected infection. This may mean SARS-CoV-2 incidence was higher than reported here with participants having an infection undetected by PCR and serology.

Rates reported in this UK cohort are comparable to those (6\%9\%, 68/992) reported in a cohort of children of UK healthcare workers during the first wave of the pandemic 2020.\textsuperscript{39} Other UK paediatric seroepidemiology studies have yet to be formally reported.\textsuperscript{26,27}

The serology rates are comparable to a cross-sectional study in Madrid from September 2020 to February 2021 in paediatric rheumatology patients where 5\%7\% (6/105) had PCR positive cases and 20\%0\% (21/105) had serology positive cases with no overlap between these groups.\textsuperscript{22} Our results are comparable to initial data from a prospective Belgian cohort study which reported 6\%0\% (15/250) serology positive participants in paediatric patients with chronic medical conditions. Only one seropositive participant, with a diagnosis of cystic fibrosis, required hospital admission while the rest were either asymptomatic or had mild symptoms.\textsuperscript{21}

These rates are higher than observed in a cross sectional study from the USA from April 2020 to May 2020 and June 2020 to July 2020. In immunocompromised paediatric patients there were 1\% (5/485) serology positive cases and 0\%4\% (2/485) PCR positive cases with one of these in both groups.\textsuperscript{25}

The reason for PCR positive cases not having detectable antibodies has not been established in our study and no associations are evident. Some evidence from inflammatory bowel disease patients suggests infliximab and other cytokine inhibitors may reduce seroconversion.\textsuperscript{23,40} Of participants with negative serology tests but prior PCR confirmed SARS-CoV-2 infection, five had juvenile idiopathic arthritis, one immunodeficiency, and one type one diabetes. The remaining two are described in Table 2 as they reported admission with SARS-CoV-2 infection.

Limited conclusions can be drawn from serology in those who received a prior dose of a COVID vaccine given the single time point and short interval between vaccination and antibody testing.

Limitations

Limitations of our study include random censoring, due to late entry or withdrawal, which was experienced by 60\% of participants. Due to this level of censoring, less confidence should be placed in results than the calculated confidence intervals. Questionnaire data is patient or parent reported and subject to recall bias, although we tried to minimize this by sending the questionnaire every week. Symptom over-reporting is possible, particularly in weeks when participants reported positive PCR tests. Symptom under-reporting is possible, particularly in participants with a baseline of symptoms from chronic disease, although less likely due to levels of anxiety in this cohort.\textsuperscript{18} Hazard of infection is likely over-estimated due to self-selection bias with participants presumably responding to surveys more frequently in weeks they reported a positive PCR swab. The shielding precautions taken will have varied both between individuals and through the course of the pandemic, so the individual hazard of SARS-CoV-2 infection will vary. The serology sub-study cohort was not representative of the overall study as described in the results section.

Following the study period reported here, in May 2021 the predominant strain in the UK became the Delta variant. There has been concern about the increased transmissibility and severity found in adults infected with the Delta variant.\textsuperscript{41} Fortunately, children have been shown to not be at increased risk of severe disease from it\textsuperscript{42}. This emphasises the need for ongoing surveillance of the impact of variant strains on the risk to immunocompromised children.

Conclusion

Though cases of COVID-19 occurred in UK immunocompromised children and young people following the cessation of shielding measures, there was no increased risk of severe SARS-CoV-2 infection in this large prospective national cohort. The serology results suggest that asymptomatic or unproven infection is quite common. Increasing age and immunodeficiency increased hazard of SARS-CoV-2 infection. Worsening of fever, cough, and sore throat were predictive of positive SARS-CoV-2 PCR.

Contributors

HC, RP, and HdG drafted and revised the manuscript. All authors reviewed and approved the final manuscript as submitted. HC, RP, CD, LM, MS, DG, AL, JS, SNF, all ImmunoCOVID study group members and HdG contributed to the recruitment of participants. CD completed statistical analysis and contributed to the statistical analysis section and tables of the manuscript. AT, WI, PT, HJ, and TH-C completed laboratory analysis of serology samples and AT, WI, and PT contributed to the serology sections of the manuscript.

Dissemination declaration

We plan to disseminate the results to study participants and their parents.
Data sharing statement
Research data may be made available upon reasonable request, wherever legally and ethically possible.

Transparency declaration
The Corresponding Author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted. Any discrepancies from the study as planned have been explained.

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Declaration of Competing Interest
All authors have completed ICMJE disclosure forms. HDG received grant funding from the BPAIG for the submitted work; there are no other relationships or activities that could appear to have influenced the submitted work.

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Supplementary materials
Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2021.11.005.

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