



BMJ Open COVID-19 symptom surveillance in immunocompromised children and young people in the UK: a prospective observational cohort study

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ABSTRACT

Objectives To describe the frequency of symptoms compatible with SARS-CoV-2 infection in immunocompromised children and young people in the UK during the SARS-CoV-2 pandemic. To describe patient/parent anxiety regarding SARS-CoV-2 infection in this cohort.

Design A prospective observational cohort study.

Setting 46 centres across the UK between 16 March and 4 July 2020. A weekly online questionnaire based on the International Severe Acute Respiratory and emerging Infections Consortium-WHO Case Report Form was used to collect participant reported data on symptoms, test results, National Health Service attendance, hospital admission and impact on daily life.

Participants 1490 immunocompromised children, defined as those requiring an annual influenza vaccination due to their underlying condition or medication.

Main outcome measures Incidence of SARS-CoV-2-like symptoms and patient/parent anxiety score.

Results Over 16 weeks during the first wave of the pandemic, no SARS-CoV-2 infection was diagnosed in this large immunocompromised paediatric cohort (median age 11 years, 54.4% female). 110 symptomatic participants underwent a test for SARS-CoV-2; all were negative. 922 (67.4%) participants reported at least one symptom consistent with suspected SARS-CoV-2 infection over the study period. 476 (34.8%) reported three or more symptoms. The most frequently reported symptoms included joint pain, fatigue, headache, nausea and muscle pain. SARS-CoV-2 testing during this period was performed on admitted patients only. 137 participants had their medication suspended or changed during the study period due to assumed COVID-19 disease risk. 62% reported high levels of anxiety (scores of 7–10 out of 10) at the start of the study, with anxiety levels remaining high throughout the study period.

Conclusions Although symptoms related to SARS-CoV-2 infection in children were common, there were no positive tests in this large immunocompromised cohort. Symptom-based screening to facilitate early detection of SARS-CoV-2 infection may not be helpful in these individuals. Patient/parent anxiety about SARS-CoV-2 infection was high.

Trial registration number NCT04382508.

Strengths and limitations of this study

- Large prospective cohort of immunocompromised children.
- High response rate of patients to questionnaire.
- Patient reported data.
- Limited SARS-CoV-2 testing due to shortage in national supply.

INTRODUCTION

COVID-19 is an ongoing global health crisis with over 11 500 000 cases and in excess of 500 000 deaths worldwide. The illness is caused by SARS-CoV-2. As of 5 August 2020, the WHO reported 306 297 cumulative cases of confirmed SARS-CoV-2 infection in the UK population of 68.1 million, giving a cumulative incidence of 0.004%.¹

SARS-CoV-2 causes mild or moderate upper respiratory tract infection in the majority of children, with fever and cough being the most common symptoms, although many are asymptomatic.² In children, fewer cases of SARS-CoV-2 infection have been reported compared with adults.³ However, it remains unclear how many children in the community have been infected, with the results of seroprevalence studies awaited.⁴

Data demonstrating an increased risk of severe disease in immunocompromised adults are emerging (A Richter, personal communication 2020, publication submitted). Children with significant comorbidities are also currently considered to be at higher risk of severe infection. They were given specific precautionary advice when UK lockdown was applied, to slow the spread of SARS-CoV-2, on 23 March 2020.^{5 6}

The primary objective of this study is to describe the frequency of symptoms compatible with SARS-CoV-2 infection in

immunocompromised children and young people, a subset of the population in whom there is limited reported data. A secondary objective of this study is to describe patient/parent anxiety regarding SARS-CoV-2 infection.

METHODS

In this prospective cohort study, immunocompromised patients under 18 years were identified by the clinical teams at 46 hospitals across the UK (online supplemental appendix B). Children and young people were considered to be immunocompromised if they required an annual influenza vaccination due to their underlying condition or medication, following the immunisation against infectious disease UK government guidance.⁷

Patient and public involvement (PPI)

Study design included PPI. Parents of children on immunosuppressive drugs were asked about their willingness to participate in such a study and whether they had any specific questions or anxieties.

Parents and participants were sent age-appropriate patient information sheets and asked to complete an online consent form. If they did not reply after receiving electronic reminders in the following 3 weeks, they were removed from the study database. Following completion of online consent, participants were sent a weekly online questionnaire based on the International Severe Acute Respiratory and emerging Infections Consortium and WHO COVID-19 Case Report Form,⁸ with questions also incorporating PPI feedback (online supplemental appendix C: weekly questionnaire). Depending on the age and ability of the child or young person, questionnaires were either completed by the participant or their parent or carer.

From 16 March 2020, information was collected regarding symptom presentation, test results, National Health Service (NHS) attendance, hospital admission and the effects of COVID-19 on daily life. Loss of smell or taste was added to the weekly questionnaire at week 14

following emerging evidence for anosmia and ageusia in COVID-19 disease. Study participants were advised that the study did not replace normal healthcare provision and were asked to follow government guidance and seek medical advice via emergency healthcare providers or the child's normal clinical team if concerns about symptoms arose. The study team did not provide advice on SARS-CoV-2 testing. During the study period, in the UK testing was limited to patients possibly needing admission (due to national testing capacity).

Study recruitment closed on 4 July 2020. Data collection is ongoing, and follow-up is planned to continue for 12 months.

Statistical analysis

Longitudinal data were collected as participants were asked to complete a weekly online questionnaire for 1 year. We report data up to the 4 July 2020, when lockdown restrictions in the UK were eased. All questionnaire data collected over this 16-week study period were included in the analysis, although some participants did not complete the questionnaire every week. Participants who did not complete any questionnaires were not included in the analysis. Analysis assumed that the date of entry into the study was the date of the first completed questionnaire. Data were cleaned and analysed every week, and a top-level report was provided to NHS England and the Royal College of Paediatrics and Child Health. The descriptive statistics presented in this paper were analysed using SAS V.9.4. Spearman correlation was used to analyse the correlation between anxiety scores and number of symptoms.

RESULTS

Recruitment increased over the 16-week study period (figure 1). By week 16, 1490 eligible patients or their parents had consented. Weekly online questionnaire response rate varied between 74% and 100% (figure 1). The median age of participants was 11 years (range 0–18 years), 54.5% of participants were female. Baseline

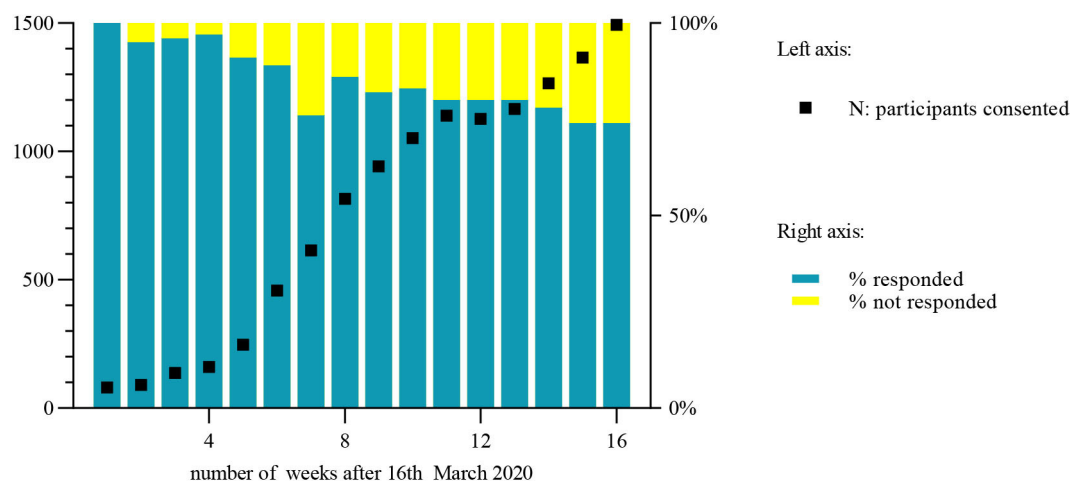


Figure 1 Study recruitment and weekly questionnaire response rate.

Table 1 Baseline characteristics: primary diagnosis and medication

	Male	Female	Total
	N (%)	N (%)	N (%)
Primary diagnosis			
Juvenile idiopathic arthritis	140 (20.6)	314 (38.7)	454 (30.5)
Other rheumatological diagnoses	48 (7.1)	110 (13.6)	158 (10.6)
Immunodeficiency disorders	64 (9.4)	53 (6.5)	117 (7.9)
Solid organ or bone marrow transplant	53 (7.8)	36 (4.4)	89 (6.0)
Renal disease	56 (8.2)	27 (3.3)	83 (5.6)
Malignant haematology and oncological diagnoses	51 (7.5)	28 (3.5)	79 (5.3)
Airways disease	29 (4.3)	24 (3.0)	53 (3.6)
Inflammatory bowel disease	29 (4.3)	23 (2.8)	52 (3.5)
Diabetes	30 (4.4)	19 (2.3)	49 (3.3)
Neurological diagnoses	20 (2.9)	10 (1.2)	30 (2.0)
Other gastroenterology and hepatology diagnoses	7 (1.0)	12 (1.5)	19 (1.3)
Other	26 (3.8)	34 (4.2)	60 (4.0)
Missing diagnosis	126 (18.6)	121 (14.9)	247 (16.6)
Total	679 (45.6)	811 (54.4)	1490 (100)
Medication			
Methotrexate	137 (20.2)	249 (30.7)	386 (25.9)
Anti-Tumor Necrosis Factor therapy	101 (14.9)	202 (24.9)	303 (20.3)
Corticosteroids	134 (19.7)	115 (14.2)	249 (16.7)
Other antibiotics and antivirals	105 (15.5)	63 (7.8)	168 (11.3)
Calcineurin inhibitors	87 (12.8)	71 (8.8)	158 (10.6)
Mycophenolate mofetil	64 (9.4)	67 (8.3)	131 (8.8)
Other disease-modifying antirheumatic drugs	56 (8.2)	53 (6.5)	109 (7.3)
Inhalers	46 (6.8)	40 (4.9)	86 (5.8)
Insulin	46 (6.8)	36 (4.4)	82 (5.5)
Non-steroidal anti-inflammatory drugs	21 (3.1)	51 (6.3)	72 (4.8)
Chemotherapy	41 (6.0)	27 (3.3)	68 (4.6)
Azithromycin	40 (5.9)	28 (3.5)	68 (4.6)
Hydroxychloroquine	11 (1.6)	44 (5.4)	55 (3.7)
Tocilizumab	16 (2.4)	33 (4.1)	49 (3.3)
Intravenous or subcutaneous immunoglobulin	21 (3.1)	17 (2.1)	38 (2.6)
Other biological drugs	14 (2.1)	22 (2.7)	36 (2.4)

characteristics of participants are shown in [table 1](#). When participants had more than one diagnosis, the primary diagnosis is reported.

Information regarding primary diagnosis was incomplete for 247 (16.6%) participants. Of 1368 participants who completed at least 1 weekly online questionnaire, 922 (67.4%) reported at least one symptom consistent with suspected SARS-CoV-2 infection over the study period. Four hundred and seventy-six (34.8%) reported three or more simultaneous symptoms. The most frequently reported symptoms included joint pain, fatigue, headache, nausea and muscle pain. Symptoms according to primary diagnosis and medication can be found in online supplemental appendix D.

[Figure 2A](#) depicts the relationship between cough, fever, sore throat and shortness of breath, with some degree of overlap between these symptoms. The frequency of cough, blocked nose and sore throat decreased in both airways and non-airways disease participants over the study period ([figure 2B and C](#)). This trend was more marked in those with airways disease ([figure 2B](#)).

Fifty-three participants (3.9%) visited primary or secondary NHS care due to concerns about SARS-CoV-2 infection, of whom 47 (88.7%) reported symptoms. Two participants were admitted to hospital. One hundred and thirty-five participants (9.9%) underwent a viral PCR test for SARS-CoV-2 infection. One hundred and ten of these reported symptoms. None of the study participants tested

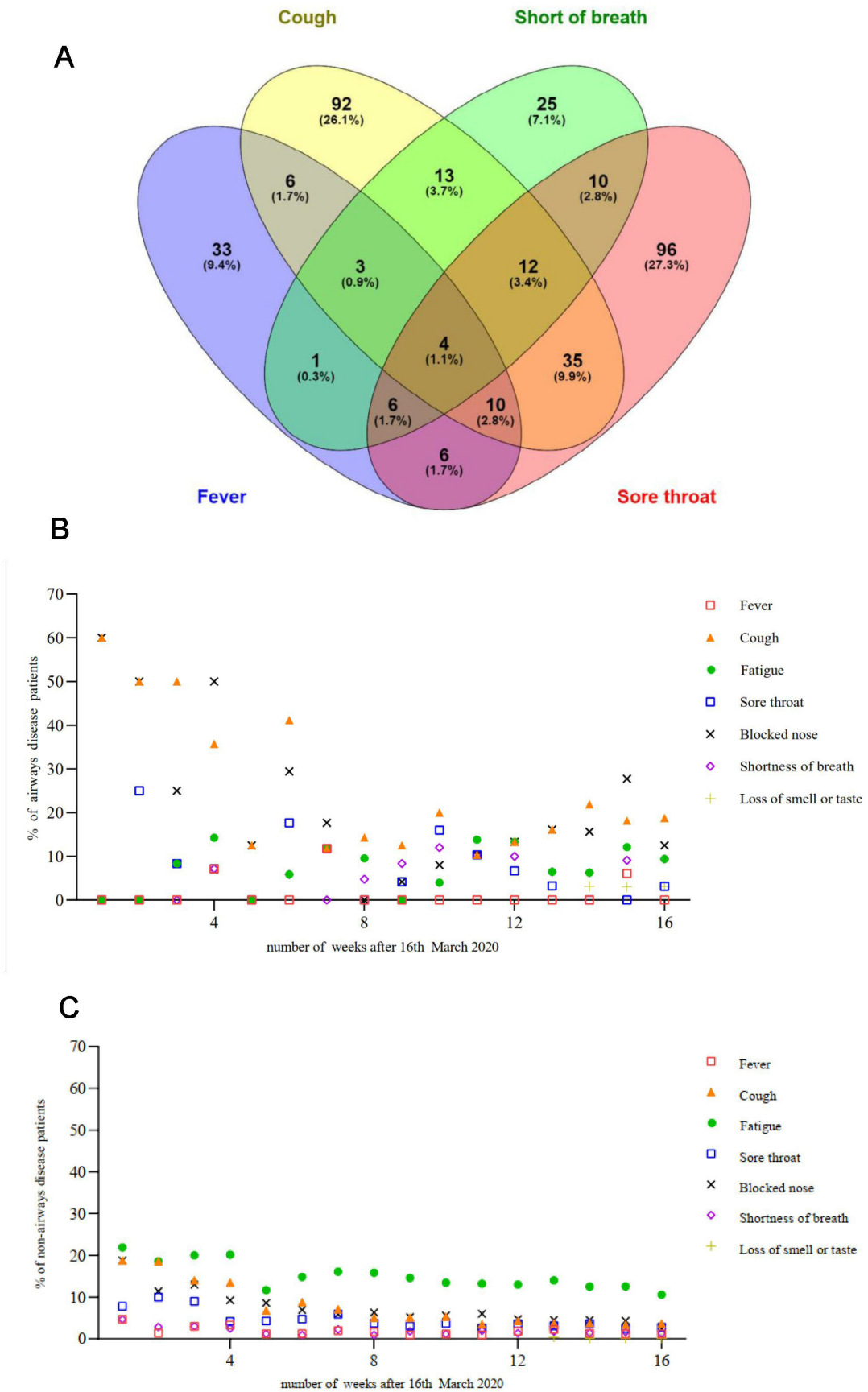


Figure 2 (A) Venn diagram depicting the association between fever, cough, shortness of breath and sore throat during the study period. (B) Reported symptoms in airways disease patients over time. (C) Reported symptoms in non-airways disease patients over time.

positive for SARS-CoV-2 infection. One hundred and thirty-seven participants had their medication suspended or changed during the study period due to assumed risk of SARS-CoV-2 disease. Of these 117 (85.4%) reported symptoms.

Figure 3A illustrates relatively static low school attendance over the 16-week study period, during which schools were closed to the majority of children. Sixty-two per cent of questionnaire respondents reported high levels of anxiety (scores of 7–10 out of 10) at the start of the study, with anxiety levels remaining extremely high throughout (figure 3B). With the easing of lockdown restrictions in July 2020, anxiety themes included concerns regarding the severity of SARS-CoV-2 infection, the reopening of schools and a second wave of infection. The correlation between number of symptoms and anxiety was not significant using cross-sectional Spearman correlation.

DISCUSSION

While 922 (67.4%) participants reported one or more symptoms consistent with suspected SARS-CoV-2 infection, of the 110 who underwent viral PCR testing, none tested positive for SARS-CoV-2, suggesting an absence of symptom specificity.²

Symptoms of SARS-CoV-2 infection overlap with those of chronic disease exacerbations and medication side effects. Joint pain was frequently reported, reflecting the contribution of rheumatological diagnoses to the cohort. This suggests symptom-based screening for SARS-CoV-2 infection may not be helpful in these immunocompromised children and young people.

We are unable to comment on the incidence rate of SARS-CoV-2 infection in this cohort without comprehensive serological data. However, we can assume that only mild cases of SARS-CoV-2 infection were missed, as none of these ‘high risk’ patients had severe enough SARS-CoV-2 infection to require hospital admission. This study period encompassed the peak in confirmed SARS-CoV-2 cases in the UK, during which time many immunocompromised children were shielding. Either shielding measures were effective, or like healthy children, immunocompromised children are less affected by SARS-CoV-2 infection than adults.^{9 10}

In the UK, of the 651 children with laboratory confirmed SARS-CoV-2, between 17 January and 3 July 2020, only 48 (8%) had a haematological, oncological or immunological comorbidity.¹¹ There was no significant difference in the presenting symptoms of the immunocompromised compared with the rest of the paediatric cohort (O Swann, personal communication 2020). Limited data for paediatric oncology, liver transplant, chronic kidney disease and inflammatory bowel disease patients are reassuring, with few cases of mostly mild infection reported.^{12–16} While some studies show adult patients on immunosuppressive biologicals may not be at higher risk of severe disease,¹⁷ other analyses suggest that adults with malignancy, autoimmune conditions, asplenia and

other immunosuppressive conditions are at greater risk of COVID-19 related death.¹⁸ However, the contribution of immunosuppression to SARS-CoV-2 disease severity in children remains unclear due to the low prevalence of severe disease in this age group.¹⁹

The frequency of cough, blocked nose and sore throat decreased in both airways and non-airways disease participants over the study period. This may suggest that shielding measures may have been effective in reducing the transmission of respiratory viruses in these children, similar to other studies.²⁰ However, this observation is unsupported by serological data.

Fifty-three participants sought NHS attention, and only two were admitted to hospital, in keeping with reports that the proportion of vulnerable paediatric inpatients has significantly decreased during the pandemic.²¹ This implies that either families were successfully managing minor or chronic symptoms at home, or they were not accessing healthcare appropriately. A decrease in attendances to paediatric emergency departments has been reported in the UK following the start of the pandemic.²² While concerns were initially raised about delayed presentations of serious illness,²³ a formal survey found this to be rare.²⁴ It may also be possible that the reduction in ‘normal’ upper and lower respiratory infection transmission prevented by self-isolation and increased hand hygiene during the lockdown period has had the indirect effect of also reducing other reported minor or chronic symptoms in this cohort.

More than 50% of questionnaire respondents reported high levels of anxiety at the start of the study, similar to national figures.²⁵ However, anxiety scores remained extremely high during this study, whereas average anxiety scores nationally reduced from 5.2 to 4.0 out of 10 by May 2020.²⁵ With the advice to stop shielding from 31 July 2020, the planned reopening of schools in September 2020 and uncertainty regarding a second wave of infection, these families require up-to-date, evidence-based guidance on the need for specific precautionary measures. If such evidence is not available, a holistic, child-centred approach must be taken by clinicians on a case-by-case basis.⁶

Study limitations include patient or parent reported information, unverified by clinical review. Inconsistent completion of weekly questionnaires over the study period may have affected the data, although a median response rate of 83% (range 74%–100%) is high for a questionnaire study. Over-reporting of symptoms may have occurred particularly as anxiety levels were high. Under-reporting of symptoms may also have occurred due to the nature of the study, which required weekly participation. Only 110 out of 922 participants with symptoms underwent viral PCR testing; therefore, some cases of mild SARS-CoV-2 infection may have been missed.

During the initial weeks of the outbreak, viral PCR tests were only performed if a child was admitted to hospital. Although all subspecialties in each hospital were approached to take part in the study, not all decided to

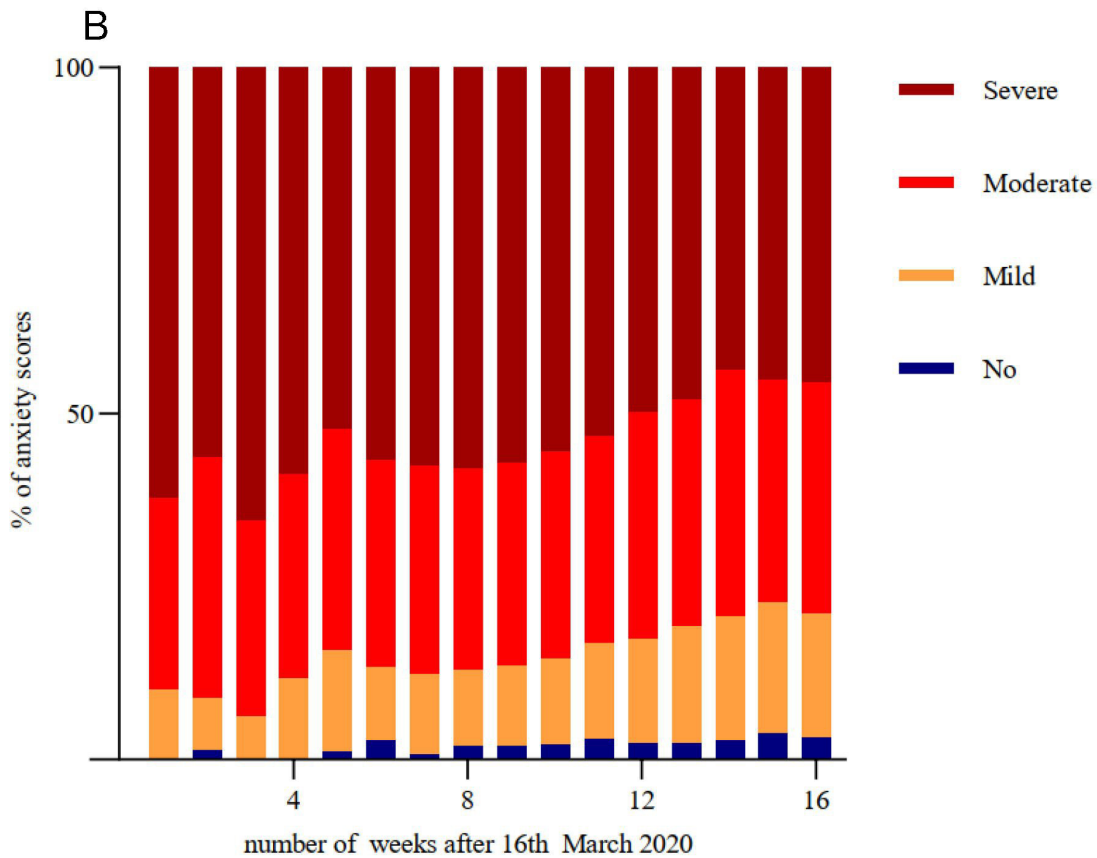
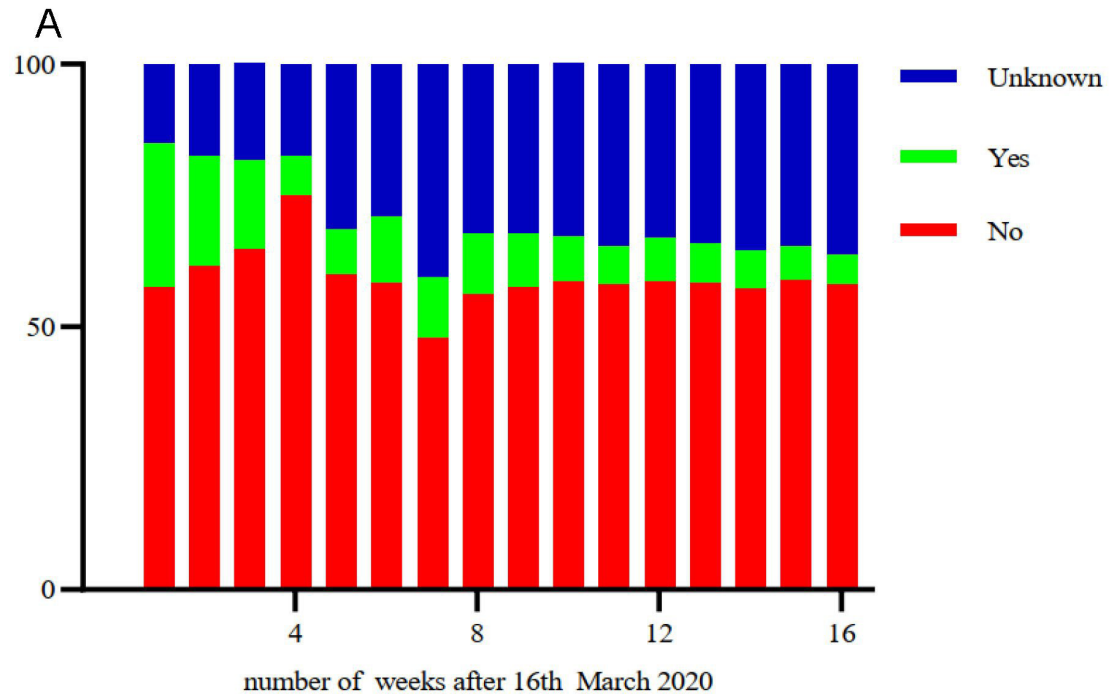


Figure 3 (A) Reported school attendance over time. (B) Reported anxiety levels over time. Anxiety scores out of 10 categorised into mild (1–3), moderate (4–6) and severe (7–10) anxiety, with a score of 0 indicating no anxiety.

participate. This may have caused bias in the composition of the cohort.

Information on SARS-CoV-2 prevalence, progression and outcomes in children is still limited, with the results of national surveillance programmes awaited. Whether children with pre-existing comorbidities are more likely to contract SARS-CoV-2 infection remains unclear. Further research is warranted to identify risk factors for severe infection in children and young people to aid health service planning, improve public health messaging and minimise unforeseen consequences of imposed restrictions on child health and well-being.

In conclusion, this is the first study to prospectively observe a cohort of immunocompromised paediatric patients during the COVID-19 pandemic. We report results from a large cohort of 1490 patients over 16 weeks. Although symptoms indicative of SARS-CoV-2 infection were common in this cohort of immunocompromised children and young people, none of these 'high risk' patients had severe SARS-CoV-2 infection requiring hospital admission. While this observation is reassuring, clinicians need to remain cautious when counselling families as symptom-based screening to facilitate the early detection of SARS-CoV-2 infection may not be helpful. In addition, these patients/parents remain very anxious, highlighting the pressing need to clearly define and communicate SARS-CoV-2 risk in children and young people.

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Collaborators The ImmunoCOVID19 study group (a full list of coauthors is provided in Supplementary Online Appendix A).

Contributors RP, HdG and SF planned the study. RP, MS and HdG managed the study and contributed to all parts of the manuscript. LM managed the patient data. CD provided statistical analysis. AL, DG, DO, JSL and SF contributed to managing the study and the writing, reviewing and editing of the manuscript. All members of the ImmunoCOVID group assisted with patient recruitment.

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