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COVID-19 symptom surveillance in immunocompromised children and young people

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ABSTRACT

Objectives: To assess the frequency and severity of SARS-CoV-2 infection in immunocompromised children and young people in the United Kingdom during the SARS-CoV-2 pandemic.

Design: A prospective observational cohort study.

Setting: 46 centres across the United Kingdom between 16th March and 4th July 2020. A weekly online questionnaire based on the ISARIC-WHO Case Report Form was used to collect participant reported data on symptoms, test results, NHS 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 infection, incidence of SARS-CoV-2 related symptoms and impact on health services and wellbeing.

Results: The median age was 11 years (range 0 – 18 years), 54.4% were female. The most common primary diagnoses were rheumatological (41.1%), immunodeficiency (7.9%) and solid organ or bone marrow transplant diagnoses (6%). Methotrexate (25.9%), anti-TNF therapy (20.3%) and corticosteroids (16.7%) were most commonly prescribed. 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. 110 symptomatic participants underwent a test for SARS-CoV-2. All were negative. The frequency of cough, blocked nose and sore throat decreased in both airways and non-airways disease participants over the study period. This trend was more marked in those with airways disease. 53 participants attended the NHS and 2 were admitted to hospital. Reported parental anxiety scores remained extremely high throughout the study period.

Conclusions: There were no positive tests for SARS-CoV-2 infection, although symptoms suggestive of SARS-CoV-2 were common. This implies that either self and family isolation (shielding) measures have been effective, or similar to healthy children, immunocompromised children are less affected by SARS-CoV-2 infection than adults. Anxiety about SARS-CoV-2 infection remains extremely high.

Trial registration: NCT04382508

Strengths

- First study to monitor a cohort of immunocompromised children of this size (1490 participants)
- The study period encompasses the height of the epidemic in the UK and subsequent lockdown period.

Limitations

- Self-reported information is unverified by clinical review
- Inconsistent completion of weekly questionnaires over the study period although this is offset by high median response rate (83%)

SUMMARY BOX

What is already known on this topic

- Fewer cases of SARS-CoV-2 infection have been reported in children and young people compared to adults.
- However, information on SARS-CoV-2 prevalence, progression and outcome in this age group is still limited.
- In addition, whether children and young people with pre-existing co-morbidities are more likely to contract SARS-CoV-2 infection remains unclear.

What this study adds

- There were no positive tests for SARS-CoV-2 infection in a large cohort of 1490 immunocompromised children and young people between March and July 2020.
- The frequency of cough, blocked nose and sore throat decreased during this time period, suggesting that shielding measures may have been effective in reducing the transmission of respiratory viruses in these individuals.
- Parents of immunocompromised children and young people report high levels of anxiety regarding SARS-CoV-2 infection.

INTRODUCTION

The 2019 coronavirus pandemic (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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of 5th August 2020, the World Health Organisation (WHO) reported 306,297 cumulative cases of confirmed SARS-CoV-2 infection in the United Kingdom (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 to 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, publication submitted). Children with significant co-morbidities 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 23rd March 2020 [5,6].

The primary objective of this study is to assess the frequency and severity of SARS-CoV-2 infection in immunocompromised children and young people, a subset of the population in whom there is limited reported data.

METHODS

In this prospective cohort study, immunocompromised patients under 18 years were identified by the clinical teams at 46 centres across the UK. Children and young people were considered to be immunocompromised if they required an annual influenza vaccination due to their underlying condition or medication. Study design

included patient and public involvement (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 three 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 (ISARIC) and WHO COVID-19 Case Report Form [7], with questions also incorporating PPI feedback (Supplementary Online Appendix B: 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 16th March 2020, information was collected regarding symptom presentation, test results, 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 recruitment closed on 4th July 2020. Data collection is ongoing and follow up is planned to continue for 12 months. The study was approved by the Leeds NHS Research Ethics Committee (IRAS 281544).

Statistical Analysis

Longitudinal data were collected as participants were asked to complete a weekly online questionnaire for one year. We report data up to the 4th 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 provided to NHS

England and the Royal College of Paediatrics and Child Health (RCPCH). The descriptive statistics presented in this paper were analysed using SAS9.4.

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 characteristics of participants are shown in Table 1.

Table 1: Baseline characteristics: primary diagnosis and medication

	Male n (%)	Female n (%)	Total 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 & 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 & 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-TNF 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 (MMF)	64 (9.4%)	67 (8.3%)	131 (8.8%)
Other disease modifying anti-rheumatic 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 (NSAIDs)	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 biologic drugs	14 (2.1%)	22 (2.7%)	36 (2.4%)
Total	**679**	**811**	**1490**

Information regarding primary diagnosis was incomplete for 247 (16.6%) participants. Of 1368 participants who completed at least one weekly online questionnaire, 922 (67.4%) reported at least one symptom consistent with suspected SARS-CoV-2 infection over the study period. 476 (34.8%) reported 3 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 Supplementary Online Appendix C.

Heat map visualisation of the dataset suggests a degree of association between certain symptom pairs (Figure 2a). 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 2c). This trend was more marked in those with airways disease (Figure 2b).

53 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. 135 participants (9.9%) underwent a viral PCR test for SARS-CoV-2 infection. 110 of these reported symptoms. None of the study participants tested positive for SARS-CoV-2 infection. 137 participants had their medication suspended or changed during the study period, of whom 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. 62% of questionnaire respondents reported high levels of anxiety (scores of 7 to 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 re-opening of schools and a second wave of infection.

DISCUSSION

While 922 (67.4%) participants reported one or more symptoms consistent with suspected SARS-CoV-2 infection, no participant tested positive for SARS-CoV-2,

suggesting an absence of symptom specificity [2] and emphasising that these patients did not have severe SARS-CoV-2 infection needing 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. In addition, during the initial weeks of the outbreak, viral PCR tests were only performed if a child was admitted to hospital. As only 9.9% of participants were tested, some cases of mild SARS-CoV-2 disease may have been missed.

In the UK, of the 651 children with laboratory confirmed SARS-CoV-2, between 17th January and 3rd July 2020, 375 (57.6%) did not have an underlying co-morbidity [8]. In the United States, the majority of children admitted to intensive care with SARS-CoV-2 infection had a pre-existing co-morbidity [9].However, the contribution of co-morbidity to SARS-CoV-2 disease severity remains unclear due to the low prevalence of severe disease in this age group [10]. Limited data for paediatric oncology, liver transplant, chronic kidney disease (CKD) and inflammatory bowel disease (IBD) patients is reassuring, with few cases of mostly mild infection reported [11-14].

The fact that the frequency of cough, blocked nose and sore throat decreased in both airways and non-airways disease participants over the study period suggests that shielding measures may have been effective in reducing the transmission of respiratory viruses in these children [15]. Overall, participants showed few symptoms specific for SARS-CoV-2 disease, had few hospital admissions and had no positive tests for SARS-CoV-2 infection. This was despite the study period occurring at the height of the pandemic in the UK, which may also suggest that similar to healthy children, immunocompromised children are less affected by SARS-CoV-2 infection than adults [16].

Only 53 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 [17]. 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 [18]. While concerns were initially raised about delayed presentations of serious illness [19], a formal survey found this to be rare [20]. 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 [21]. 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 [21]. With the advice to stop shielding from 31st July 2020, the planned re-opening 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% to 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.

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 co-morbidities 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 wellbeing.

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 SAR-CoV-2 infection were common in this cohort of immunocompromised children and young people, there were no positive tests for SARS-CoV-2 infection. Shielding measures appear to have been effective at reducing the frequency of respiratory tract symptoms. Despite this, parents remain very anxious, highlighting the pressing need to clearly define and communicate SARS-CoV-2 risk in children and young people.

Contributorship statement: MS, RP and HdG drafted and revised the manuscript. All authors reviewed and approved the final manuscript as submitted. All authors contributed to the recruitment of participants.

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Competing interests: All authors have completed the *ICMJE* uniform disclosure form at www.icmje.org/coi_disclosure.pdf. HdG received grant funding from the BPAIIG for the submitted work; there are no other relationships or activities that could appear to have influenced the submitted work.

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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Figure 1: Study recruitment and weekly questionnaire response rate

Figure 2: Heat map depicting association of reported symptoms during the study period

Scale of 0 – 800 representing cumulative frequency of simultaneously reported symptoms over the study period

Figure 3: Reported symptoms in airways disease patients over time

Figure 4: Reported symptoms in non-airways disease patients over time

Figure 5: Reported school attendance over time

Figure 6: Reported anxiety levels over time

Anxiety scores out of 10 categorised into mild (1 to 3), moderate (4 to 6) and severe (7 to 10) anxiety, with a score of 0 indicating no anxiety.

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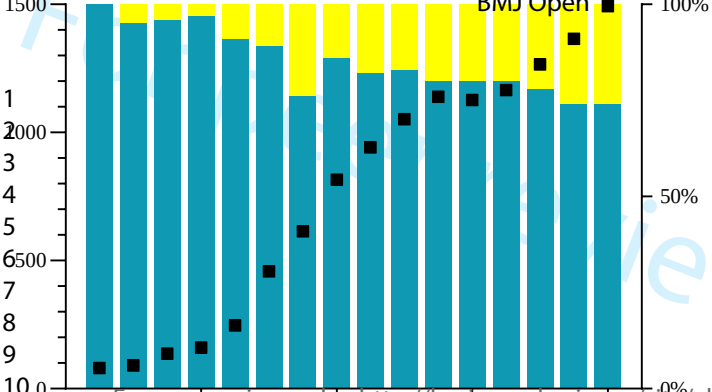

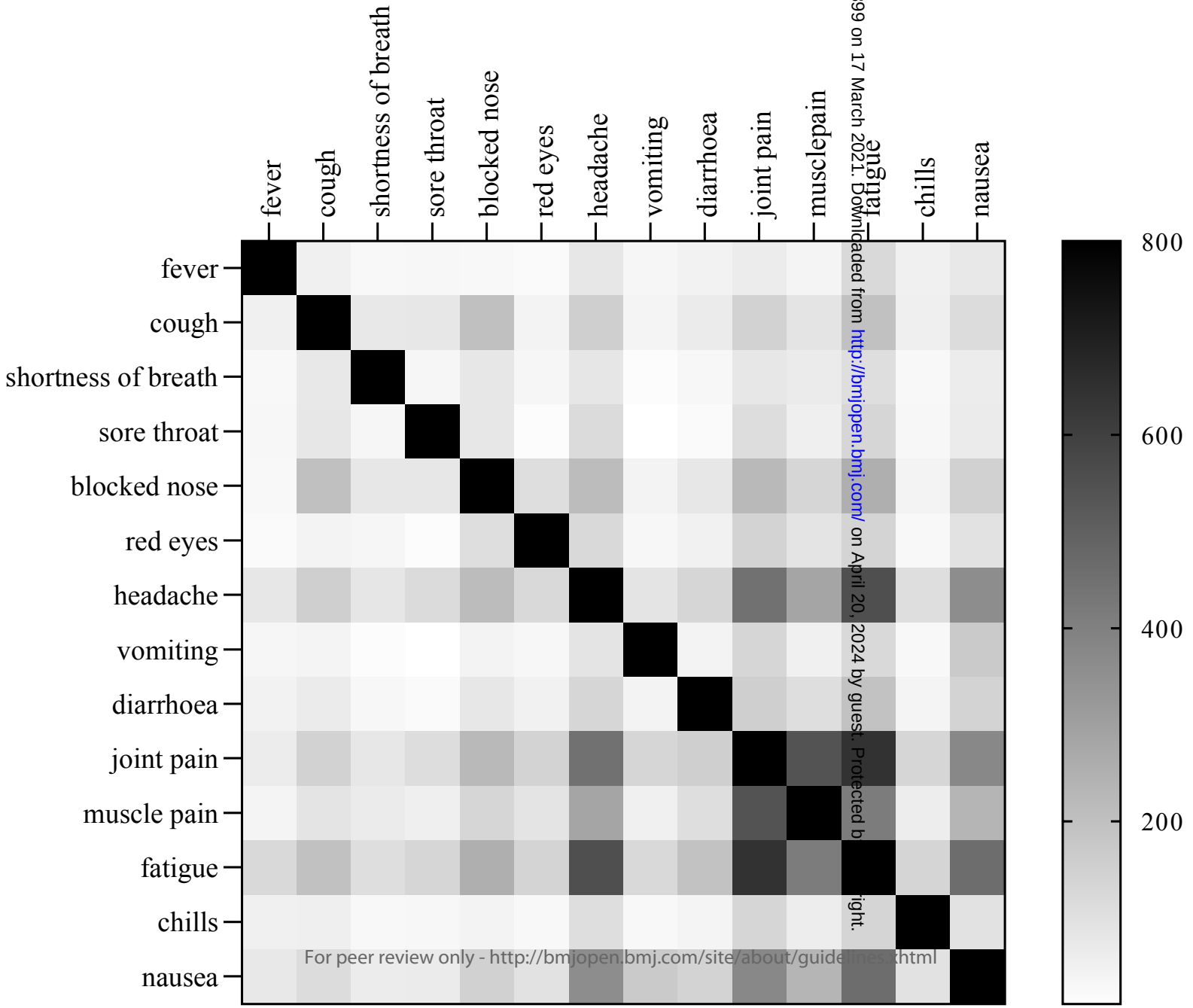

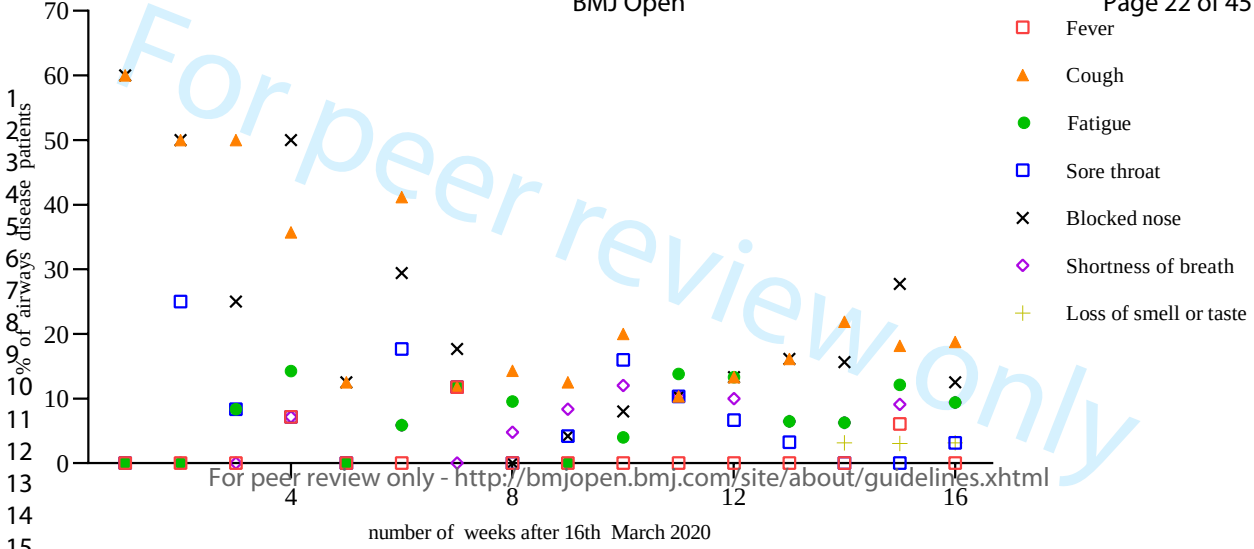

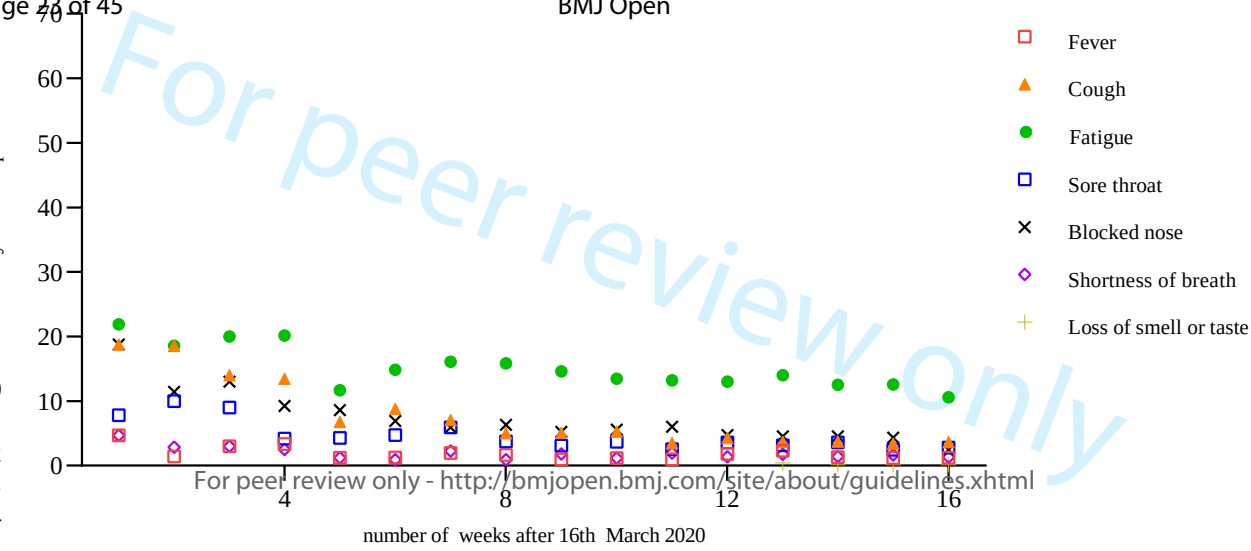

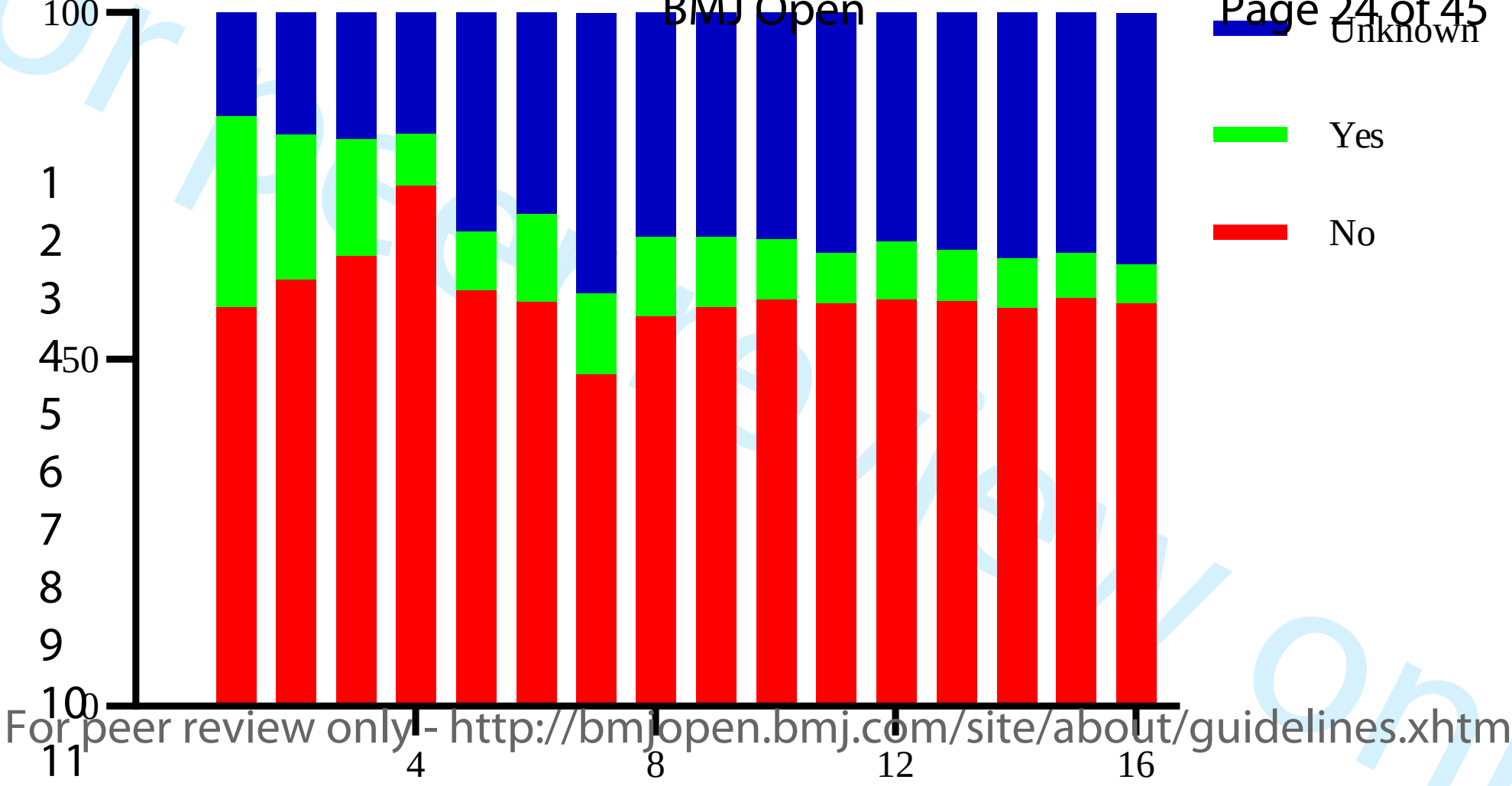

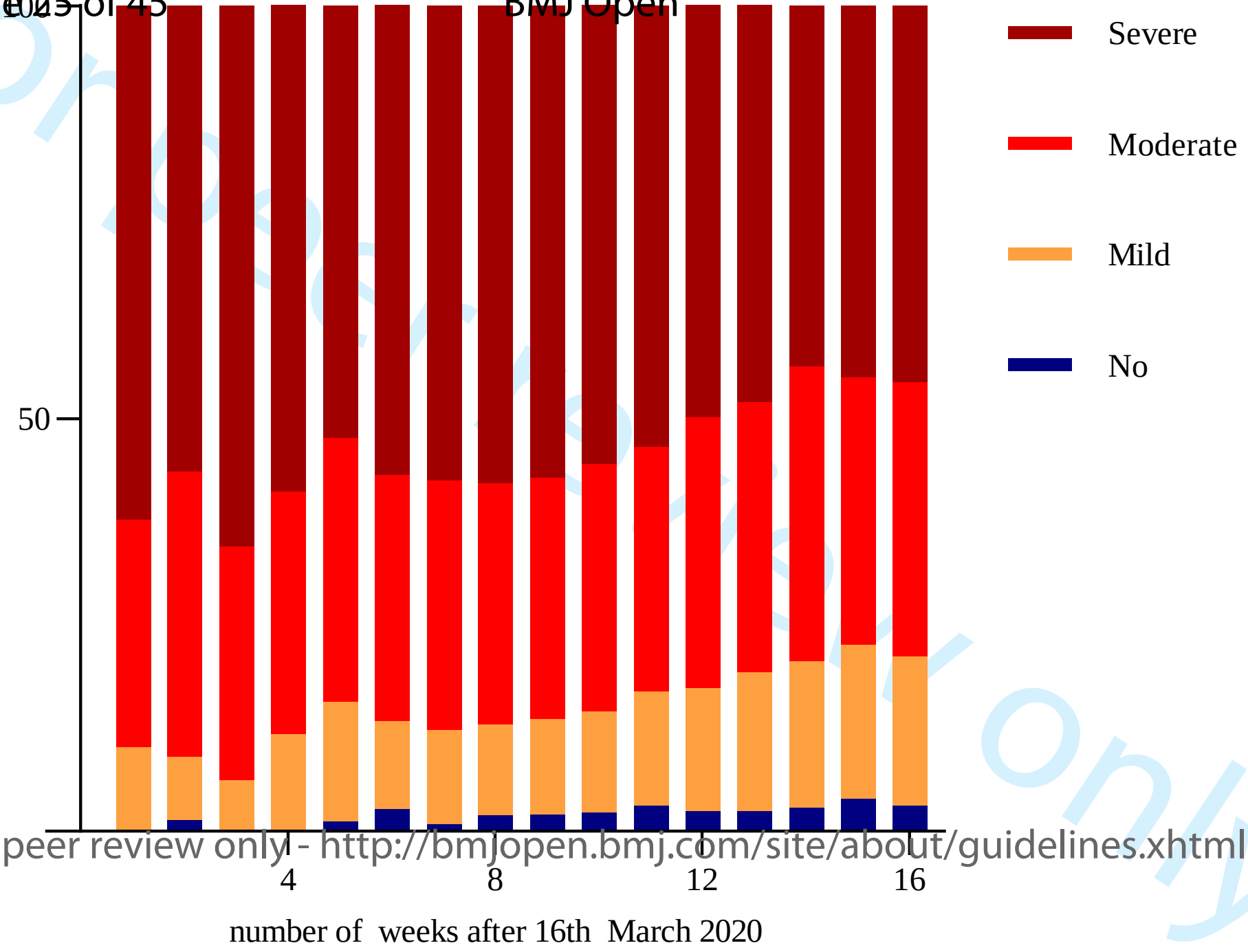

Appendix A: List of ImmunoCOVID19 Study Group Co-authors

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Appendix B: Weekly Questionnaire

In the week beginning xx/xx/xxxx have you experienced any of the following symptoms?		
1.1	I have had no symptoms	○ I have had no symptoms ○ I have had symptoms
1.2	Measured temperature above 38 °C	○ Yes ○ No
1.2.1	**If 'Measured temperature above 38 °C' is equal to 'Yes' answer this question:** Which days did you measure a temperature above 38 °C?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.2.2	**If 'Measured temperature above 38 °C' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.3	Cough	○ Yes ○ No
1.3.1	**If 'Cough' is equal to 'Yes' answer this question:** Which days did you experience a cough?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.3.2	**If 'Cough' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.4	Shortness of breath	○ Yes ○ No
1.4.1	**If 'Shortness of breath' is equal to 'Yes' answer this question:** Which days did you experience shortness of breath?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday

		☐ Sunday
1.4.2	**If 'Shortness of breath' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.5	Sore throat	○ Yes ○ No
1.5.1	**If 'Sore throat' is equal to 'Yes' answer this question:** Which days did you experience sore throat?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.5.2	**If 'Sore throat' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.6	Blocked nose	○ Yes ○ No
1.6.1	**If 'Blocked nose' is equal to 'Yes' answer this question:** Which days did you experience blocked nose?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.6.2	**If 'Blocked nose' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.7	Red eyes	○ Yes ○ No
1.7.1	**If 'Red eyes' is equal to 'Yes' answer this question:** Which days did you experience red eyes?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.7.2	**If 'Red eyes' is equal to 'Yes' answer this question:**	○ Yes ○ No

	Have you experienced a worsening of the above symptom?	
1.8	Headache	○ Yes ○ No
1.8.1	**If 'Headache' is equal to 'Yes' answer this question:** Which days did you experience headache?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.8.2	**If 'Headache' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.9	Joint pain	○ Yes ○ No
1.9.1	**If 'Joint pain' is equal to 'Yes' answer this question:** Which days did you experience joint pain?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.9.2	**If 'Joint pain' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.10	Muscle pain	○ Yes ○ No
1.10.1	**If 'Muscle pain' is equal to 'Yes' answer this question:** Which days did you experience muscle pain?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.10.2	**If 'Muscle pain' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.11	Fatigue	○ Yes ○ No

1.11.1	**If 'Fatigue' is equal to 'Yes' answer this question:** Which days did you experience fatigue?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.11.2	**If 'Fatigue' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.12	Chills	○ Yes ○ No
1.12.1	**If 'Chills' is equal to 'Yes' answer this question:** Which days did you experience chills?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.12.2	**If 'Chills' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.13	Nausea	○ Yes ○ No
1.13.1	**If 'Nausea' is equal to 'Yes' answer this question:** Which days did you experience nausea?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.13.2	**If 'Nausea' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.14	Vomiting	○ Yes ○ No
1.14.1	**If 'Vomiting' is equal to 'Yes' answer this question:** Which days did you experience vomiting?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday

		☐ Saturday ☐ Sunday
1.14.2	**If 'Vomiting' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.15	Diarrhoea	○ Yes ○ No
1.15.1	**If 'Diarrhoea' is equal to 'Yes' answer this question:** Which days did you experience diarrhoea?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.15.2	**If 'Diarrhoea' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.16	Loss of smell or taste	○ Yes ○ No
1.16.1	**If 'Loss of smell or taste' is equal to 'Yes' answer this question:** Which days did you experience loss of smell or taste?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.16.2	**If 'Loss of smell or taste' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.17	Other symptoms	
2.1	Has your child changed medication this week?	○ Yes ○ No
2.1.1	**If 'Has your child changed medication this week?" if equal to 'Yes' answer this question:** What medication has changed and how?	

2.2	Was your child in contact with someone who is diagnosed with or suspected to have coronavirus?	○ Yes ○ No ○ Not known
2.3	Did your child visit the NHS because you were worried about coronavirus infection?	○ Yes ○ No ○ Not known
2.4	Did your child have a test for coronavirus?	○ Yes ○ No ○ Not known
2.5	Did your child have a confirmed diagnosis of coronavirus infection?	○ Yes ○ No ○ Not known
2.6	Was your child admitted to hospital because of a coronavirus infection?	○ Yes ○ No ○ Not known
2.6.1	**If 'Was your child admitted to hospital because of a coronavirus infection?' is equal to 'Yes' answer this question**: When was your child admitted?	dd-mm-yyyy
2.6.2	**If 'Was your child admitted to hospital because of a coronavirus infection?' is equal to 'Yes' answer this question:** How many days was your child admitted?	
2.7	Did you have to self-isolate your child because they had symptoms or because of medical advice related to coronavirus?	○ Yes ○ No ○ Not known
2.7.1	**If 'Did you have to self-isolate your child because they had symptoms or because of medical advice related to coronavirus?' is equal to 'Yes' answer this question:** How many days did you self-isolate your child this week?	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7
2.8	Were immunosuppressive drugs postponed because of coronavirus infection?	○ Yes ○ No ○ Not known
2.8.1	**If 'Were immunosuppressive drugs postponed because of coronavirus infection?' is equal to 'Yes' answer this question**: How many days did you	☐ 1 ☐ 2 ☐ 3 ☐ 4

	postpone the immunosuppressants this week?	☐ 5 ☐ 6 ☐ 7
2.9	Did your child miss any sports or fun activities because of the coronavirus pandemic?	○ Yes ○ No ○ Not known
2.9.1	**If 'Did your child miss any sports or fun activities because of the coronavirus pandemic?' is equal to Yes answer this question:** How many activities did your child miss?	
2.10	Did your child miss school because of coronavirus infection?	○ Yes ○ No ○ Not known
2.10.1	**If 'Did your child miss school because of coronavirus infection?' is equal to Yes answer this question:** How many days of school did your child miss this week?	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7
2.11	On a scale of 0-10, how worried are you about coronavirus affecting your child? (0 = not worried, 10 = extremely worried)	
2.12	Is there anything that you are particularly worried about that you would like to share?	

Appendix C:

Symptom frequency by primary diagnosis

Symptoms	JIA (%)	Other rheumatology diagnosis (%)	Airways disease (%)	Immunodeficiency disorder (%)	Diabetes (%)	Solid organ or bone marrow transplant (%)	Nephrotic syndrome (%)	Other kidney disease (%)	IBD (%)	Other gastroenterology and hepatology (%)	Malignant haematology & oncology (%)	Neurology (%)	Other (%)
Fever	1.63	0.81	0.24	0.73	0.16	0.41	0.08	0.08	0.00	0.08	0.57	0.24	0.33
Cough	4.80	1.54	1.63	1.54	0.24	1.46	0.57	0.16	0.08	0.00	0.89	0.16	0.65
SOB	1.63	0.89	0.65	0.65	0.08	0.08	0.16	0.08	0.16	0.08	0.16	0.08	0.81
Sore throat	6.02	2.28	0.98	0.98	0.16	0.41	0.24	0.24	0.49	0.33	0.89	0.33	0.89
Blocked nose	7.48	2.60	1.79	1.30	0.49	1.30	0.65	0.41	0.73	0.82	0.57	0.24	1.22
Red eyes	4.07	2.11	0.57	1.14	0.49	0.41	0.49	0.08	0.33	0.08	0.57	0.16	0.57
Headache	11.30	4.96	1.30	2.20	0.98	1.54	0.65	0.33	0.98	0.73	1.87	0.73	1.63
Vomiting	3.66	0.89	0.33	0.65	0.08	0.89	0.24	0.24	0.00	0.49	1.14	0.08	0.98
Diarrhoea	4.23	1.63	0.57	1.46	0.49	0.81	0.33	0.33	0.81	0.16	0.73	0.24	0.73
Joint pain	19.84	3.98	0.24	1.22	0.16	1.30	0.65	0.24	0.81	0.49	1.87	0.41	1.06
Muscle pain	8.46	3.33	0.57	1.22	0.33	1.06	0.65	0.24	0.49	0.41	1.38	0.33	0.81
Fatigue	13.98	4.07	1.30	2.60	0.49	1.30	0.89	0.57	1.30	0.41	3.25	0.89	1.30
Chills	2.11	1.06	0.08	0.49	0.08	0.41	0.08	0.08	0.24	0.16	0.33	0.33	0.24

Abbreviations: SOB shortness of breath, JIA juvenile idiopathic arthritis, IBD inflammatory bowel disease

Symptom frequency by medication

Symptoms	Methotrexate (%)	Hydroxychloroquine (%)	Other DMARDs (%)	Corticosteroids (%)	Anti-TNF therapy (%)	Tocilizumab (%)	Other biologic drugs (%)	MMF (%)
Fever	4.92	9.09	0.92	5.62	4.62	4.08	11.11	5.34
Cough	12.44	14.55	9.17	14.06	15.84	4.08	8.33	15.27
SOB	3.11	3.64	1.83	6.02	4.29	8.16	5.56	4.58
Sore throat	16.06	21.82	18.35	11.24	18.15	18.37	8.33	10.69
Blocked nose	19.69	25.45	13.76	13.65	23.76	14.29	19.44	17.56
Red eyes	12.69	10.91	8.26	10.44	11.55	14.29	13.89	6.11
Headache	29.27	45.45	29.36	28.11	30.69	28.57	27.78	25.19
Vomiting	12.18	9.09	4.59	12.05	8.25	12.24	8.33	7.63
Diarrhoea	9.84	10.91	11.93	11.65	11.88	20.41	8.33	12.98
Joint pain	43.78	43.64	33.03	26.91	46.20	69.39	36.11	22.14
Muscle pain	20.98	41.82	22.02	24.50	21.45	30.61	25.00	19.08
Fatigue	39.12	43.64	29.36	34.14	34.65	40.82	38.89	24.43
Chills	5.44	12.73	5.50	7.23	6.93	6.12	5.56	6.87
Nausea	31.09	27.27	15.60	20.88	25.41	26.53	16.67	15.27
Loss of smell	0.52	1.82	0.00	0.80	0.33	0.00	0.00	1.53

Abbreviations: DMARDs disease modifying anti-rheumatic drugs, MMF mycophenolate mofetil

Symptoms	Chemotherapy (%)	Azathioprine (%)	Other antibiotics and antivirals (%)	Tacrolimus (%)	Inhalers (%)	Insulin (%)	NSAIDs (%)	IV or SC IG (%)
Fever	10.29	7.35	7.14	3.80	8.14	3.66	9.72	2.63
Cough	14.71	25.00	18.45	15.19	31.40	8.54	15.28	13.16
SOB	5.88	8.82	5.95	3.16	16.28	3.66	8.33	7.89
Sore throat	8.82	13.24	10.71	6.96	18.60	7.32	13.89	0.00
Blocked nose	10.29	16.18	13.69	14.56	36.05	9.76	25.00	10.53
Red eyes	10.29	8.82	9.52	5.70	15.12	9.76	16.67	5.26
Headache	27.94	32.35	20.83	18.35	32.56	25.61	44.44	15.79
Vomiting	22.06	10.29	14.29	8.86	12.79	7.32	9.72	5.26
Diarrhoea	14.71	10.29	13.10	10.13	12.79	10.98	12.50	5.26
Joint pain	29.41	14.71	20.24	17.09	18.60	8.54	61.11	18.42
Muscle pain	23.53	11.76	17.26	14.56	19.77	7.32	31.94	7.89
Fatigue	47.06	30.88	30.36	18.35	30.23	17.07	54.17	18.42
Chills	7.35	2.94	4.17	3.80	6.98	1.22	11.11	0.00
Nausea	30.88	19.12	17.86	12.66	20.93	10.98	27.78	10.53
Loss of smell	0.00	0.00	0.00	1.27	1.16	0.00	4.17	0.00

Abbreviations: NSAIDs non-steroid anti-inflammatory drugs, IV intravenous, SC subcutaneous, IG immunoglobulin

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	4-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-6
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	6-8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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

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On behalf of the ImmunoCOVID19 study group (a full list of co-authors is provided in Supplementary Online Appendix A)

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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 United Kingdom 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 United Kingdom between 16th March and 4th July 2020. A weekly online questionnaire based on the ISARIC-WHO Case Report Form was used to collect participant reported data on symptoms, test results, NHS 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: NCT04382508

Strengths:

- Large prospective cohort of immunocompromised children
- High response rate of patients to questionnaire

Limitations:

- Patient reported data
- Limited SARS-CoV-2 testing due to shortage in national supply

INTRODUCTION

The 2019 coronavirus pandemic (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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of 5th August 2020, the World Health Organisation (WHO) reported 306,297 cumulative cases of confirmed SARS-CoV-2 infection in the United Kingdom (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 to 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, publication submitted). Children with significant co-morbidities 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 23rd 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 (Supplementary Online

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

Study design included patient and public involvement (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 three 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 (ISARIC) and WHO COVID-19 Case Report Form [8], with questions also incorporating PPI feedback (Supplementary Online 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 16th March 2020, information was collected regarding symptom presentation, test results, 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 health care 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 testing was limited to patients possibly needing admission in the UK (due to national testing capacity).

Study recruitment closed on 4th July 2020. Data collection is ongoing and follow up is planned to continue for 12 months. The study was approved by the Leeds NHS Research Ethics Committee (IRAS 281544).

Statistical Analysis

Longitudinal data were collected as participants were asked to complete a weekly online questionnaire for one year. We report data up to the 4th 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 provided to NHS England and the Royal College of Paediatrics and Child Health (RCPCH). The descriptive statistics presented in this paper were analysed using SAS9.4. 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 characteristics of participants are shown in Table 1. When participants had more than one diagnosis, the primary diagnosis is reported.

Table 1: Baseline characteristics: primary diagnosis and medication

	Male n (%)	Female n (%)	Total 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 & 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 & 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-TNF 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 (MMF)	64 (9.4%)	67 (8.3%)	131 (8.8%)
Other disease modifying anti-rheumatic 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 (NSAIDs)	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 biologic drugs	14 (2.1%)	22 (2.7%)	36 (2.4%)

Information regarding primary diagnosis was incomplete for 247 (16.6%) participants. Of 1368 participants who completed at least one weekly online questionnaire, 922 (67.4%) reported at least one symptom consistent with suspected SARS-CoV-2 infection over the study period. 476 (34.8%) reported 3 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 Supplementary Online 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 2c). This trend was more marked in those with airways disease (Figure 2b).

53 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. 135 participants (9.9%) underwent a viral PCR test for SARS-CoV-2 infection. 110 of these reported symptoms. None of the study participants tested positive for SARS-CoV-2 infection. 137 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. 62% of questionnaire respondents reported high levels of anxiety (scores of 7 to 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 re-opening 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 requiring 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 similar to 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 17th January and 3rd July 2020, only 48 (8%) had a haematological, oncological or immunological co-morbidity [11]. There was no significant difference in the presenting symptoms of the immunocompromised compared to the rest of the paediatric cohort (O. Swann, personal communication). Limited data for paediatric oncology, liver transplant, chronic kidney disease (CKD) and inflammatory bowel disease (IBD) patients is reassuring, with few cases of mostly mild infection reported [12-16]. While some adult patients on immunosuppressive biologics 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 co-morbidity 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.

53 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 31st July 2020, the planned re-opening 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% to 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 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 co-morbidities 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 wellbeing.

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.

Contributorship statement: 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, JL 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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Ethics statement: Parental consent has been obtained for all participants under the age of 16 years.

Competing interests: All authors have completed the *ICMJE* uniform disclosure form at www.icmje.org/coi_disclosure.pdf. HdG received grant funding from the BPAIIG for the submitted work; there are no other relationships or activities that could appear to have influenced the submitted work.

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.

Figure 1: Study recruitment and weekly questionnaire response rate

Figure 2a: Venn diagram depicting the association between fever, cough, shortness of breath and sore throat during the study period

Figure 2b: Reported symptoms in airways disease patients over time

Figure 2c: Reported symptoms in non-airways disease patients over time

Figure 3a: Reported school attendance over time

Figure 3b: Reported anxiety levels over time

Anxiety scores out of 10 categorised into mild (1 to 3), moderate (4 to 6) and severe (7 to 10) anxiety, with a score of 0 indicating no anxiety.

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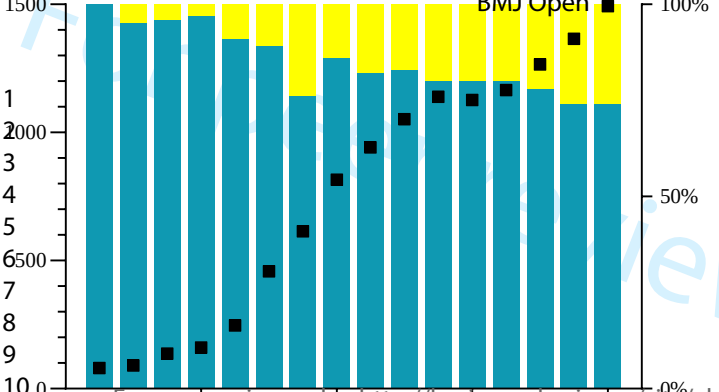

Fig 2a

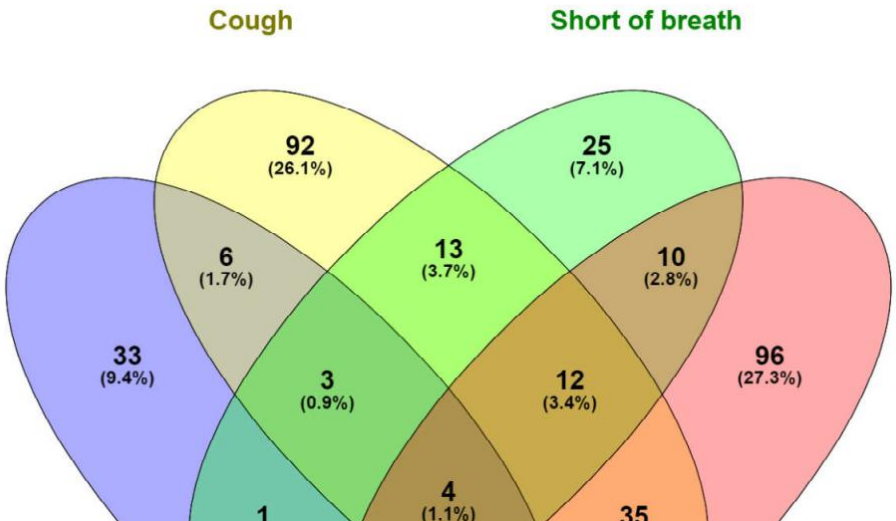

Fig 2b

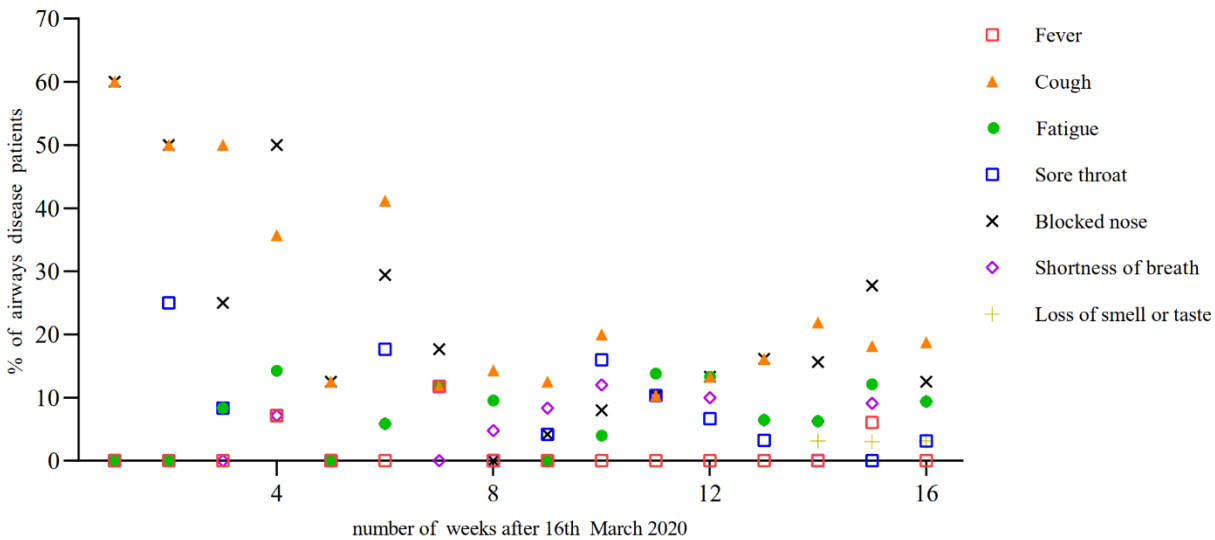

Fig 2c

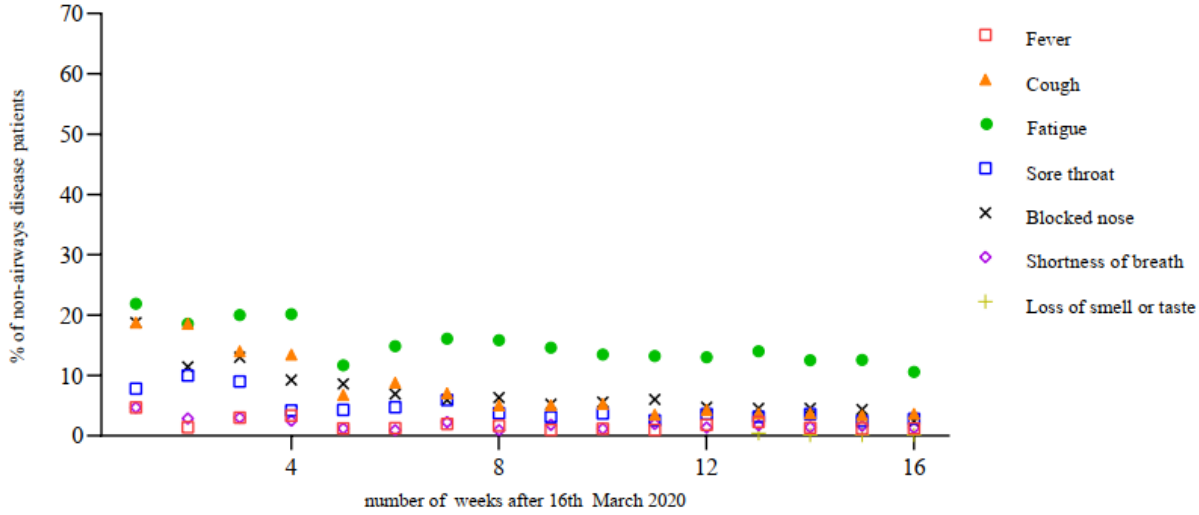

Fig 3a

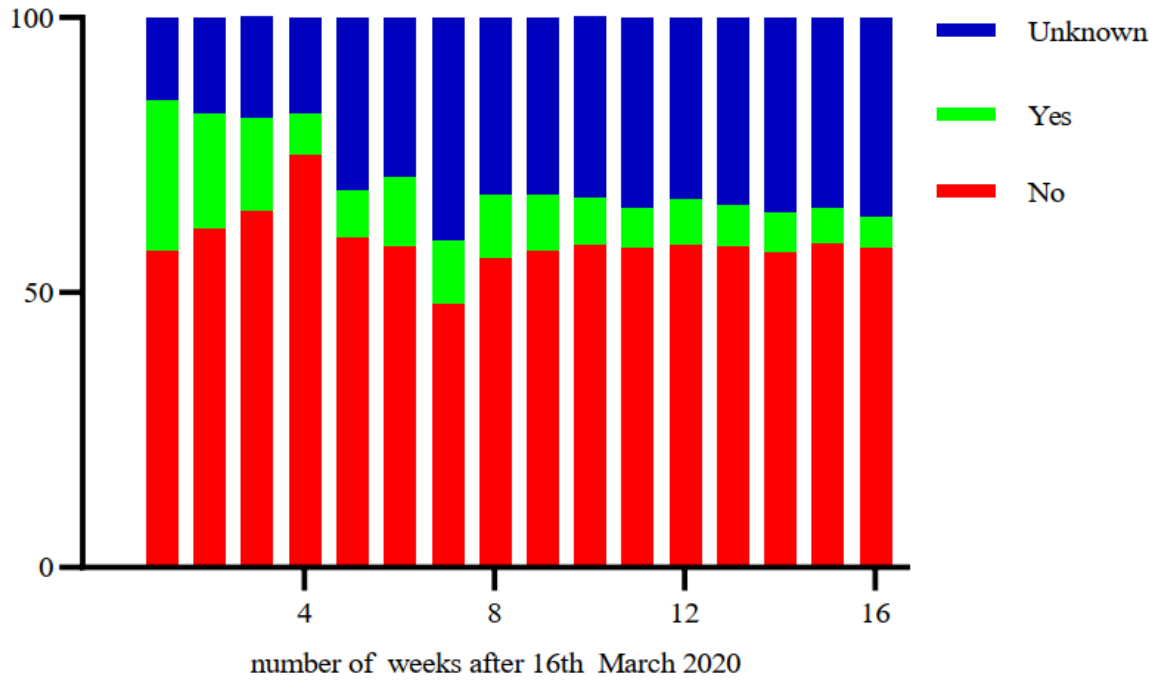
100
50
0
4
8
12
16
number of weeks after 16th March 2020
Unknown
Yes
No

Fig 3b

100
50
% of anxiety scores
4
8
12
16
number of weeks after 16th March 2020
Severe
Moderate
Mild
No

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Mrs	Sharon Davies-Dear	Clinical Trials Project Manager	R&D, University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Dr	Christian De Goede	Consultant Paediatric Neurologist	Department of Child Health, Lancashire Teaching Hospitals NHS Trusts	Royal Preston Hospital, Sharoe Green Lane, Preston PR2 9HT
Dr	Hans de Graaf	Consultant Paediatric Rheumatology	NIHR Southampton Clinical Research Facility and Paediatric Medicine, University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Dr	Samundeeswari Deepak	Consultant Paediatric and Adolescent rheumatology	Nottingham Children's Hospital, Queen's Medical Centre, Nottingham University Hospitals NHS Trust	Derby Road, Nottingham, NG72UH
Mr	Fatjon Dekaj	CLUSTER Research Coordinator	Infection, Immunity and Inflammation Research & Teaching Department, University College London Great Ormond Street Institute of Child Health	30 Guilford Street, London, WC1N 1EH
Miss	Sarah Diment	Paediatric Research Nurse	Salisbury District Hospital	Salisbury, Wiltshire, SP2 8BJ
Dr	Corine Driessens	Research Fellow	University of Southampton, Faculty of Medicine, Clinical and Experimental Sciences	Tremona Road, Southampton, SO16 6YD
Dr	Simon B Drysdale	Consultant in Paediatric Infectious Diseases and Immunology	Paediatric Infectious Diseases Research Group, St George's, University of London and St George's University Hospitals NHS Foundation Trust	Cranmer Terrace, London, SW17 0RE
Dr	Martin Elliott	Consultant paediatric Oncology	Leeds Children Hospital	Leeds Teaching Hospital NHS Trust, Great George Street, LS1 3EX
Prof	Marieke Emonts	Consultant Paediatric Infectious Diseases & Immunology, Honorary	Newcastle Hospitals NHS Foundation Trust; Translational and Clinical Research Institute, Newcastle University, and NIHR Newcastle Biomedical Research Centre based at Newcastle upon Tyne Hospitals NHS Trust and Newcastle University	Royal Victoria Hospital, Queen Victoria Road, Newcastle upon Tyne. NE1 4LP

		Professor Paediatric Infectious Diseases		
Dr	Mich Erlewyn-Lajeunesse	Consultant Paediatric Allergy and Immunology	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Dr	Hazel Evans	Paediatric Respiratory Consultant	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Mrs	Tracey Farnon	Paediatric Consultant	Salisbury District Hospital	Salisbury, Wiltshire SP2 8BJ
Prof	Saul Faust	Professor of Paediatric Immunology and Infectious Diseases	NIHR Southampton Clinical Research Facility and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and Faculty of Medicine and Institute for Life Sciences, University of Southampton	Tremona Road, Southampton, SO16 6YD
Dr	Susanna Felsenstein	Consultant Paediatric Infectious Diseases	Alder Hey Children's Hospital	Liverpool, East Prescot Rd L14 5AB
Ms	Lynsey Felton	Paediatric Research Nurse	James Paget University Hospital	Lowestoft Rd, Gorleston, NR31 6LA
Dr	Matthew Fenton	Consultant Paediatric Cardiologist	Great Ormond Street Hospital for Children NHS Foundation Trust	Great Ormond Street, London WC1N 3JH
Dr	Katy Fidler	Clinical Senior Lecturer in Paediatric Infectious Diseases and Immunology	Academic Dept of Paediatrics, Brighton and Sussex Medical School, University of Sussex	N - S Rd, Falmer, Brighton BN1 9PX
Mrs	Debbie Fisher	Trial Coordinator	Paediatric Oncology and Haematology, Cambridge University Hospitals NHS Foundation Trust	Hills Road, Cambridge, CB2 0QQ
Dr	Peter W Fowlie	Consultant Paediatrician	Ninewells Hospital and Medical School	Dundee, DD1 9SY
Mrs	Kirsty Galvin	Lead Nurse	Children's Community Nursing Team, Kent community Health Foundation Trust	Trinity House, 110-12- Upper Pemberton, Kennington, Ashford, Kent, TN25 4AZ
Ms	Emma Gardiner	Research Nurse	University Hospital Lewisham	Paediatric Offices, Nockold House, University Hospital Lewisham, Lewisham High street, London, SE13 6LH
Dr	Edward Gaynor	Paediatric Gastroenterology Consultant	Great Ormond Street Hospital for Children NHS Foundation Trust	Great Ormond Street, London WC1N 3JH
Dr	Diane Gbesemete	Clinical Research Fellow	NIHR Southampton Clinical Research Facility and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and Faculty of Medicine and Institute for Life Sciences, University of Southampton	Tremona Road, Southampton, SO16 6YD
Dr	Rodney Gilbert	Consultant Paediatric Nephrologist	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Dr	Francis J Gilchrist	Paediatric Respiratory Consultant	University Hospitals of North Midlands NHS Trust	Staffordshire Children's Hospital at Royal Stoke, Newcastle Road, Stoke on Trent, ST4 6QG
Mrs	Clare Gilmour	Immunology Clinical Nurse Specialist	St George's University Hospitals NHS Foundation Trust	Cranmer Terrace, London, SW17 0RE
Ms	Claire Glemas	Research Nurse	Paediatric Gastroenterology, Cambridge University Hospitals NHS Foundation Trust	Hills Road, Cambridge, CB2 0QQ
Dr	Emma Grainger-Allen	Consultant Paediatric Allergy and Immunology	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Dr	Juliet Gray	Associate Professor and Consultant in Paediatric Oncology	Department of Paediatric Oncology, University Hospital Southampton NHS Foundation Trust and Faculty of Medicine and Institute for Life Sciences, University of Southampton	Tremona Road, Southampton, SO16 6YD
Ms	Donna Griffiths	Paediatric Research Nurse	James Paget University Hospital	Lowestoft Rd, Gorleston, NR31 6LA
Mrs	Rowena Guermech	Research Nurse	Paediatric Oncology and Haematology, Cambridge University Hospitals NHS Foundation Trust	Hills Road, Cambridge, CB2 0QQ
Mr	Neil Hall	Research Nurse	Leeds Children Hospital	Leeds Teaching Hospital NHS Trust, Great George Street, LS1 3EX

Miss	Nicola Hamilton	Paediatric Rheumatology Link Nurse	NHS Forth Valley	Forth Valley Royal Hospital, Stirling Road, Larbert FK5 4WR
Mrs	Joanna Hancock	Clinical Nurse Specialist	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Dr	Mushfequr R Haq	Consultant Paediatric Nephrologist	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton SO16 6YD
Mrs	Amanda Harris	PCD & Children's Respiratory Clinical Nurse Specialist	NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust	
Dr	Kathryn Harrison	Consultant Paediatric & Adolescent Rheumatology	Rheumatology Department, Birmingham Children's Hospital, Birmingham Women's and Children's NHS Foundation Trust	Steelhouse Lane, Birmingham B4 6NH
Ms	Rebecca Harrop	Data Manager	Great North Children's Hospital	Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP
Miss	Sarah Hartfree	Paediatric Rheumatology Clinical Nurse Specialist	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton SO16 6YD
Mrs	Laura Hennelly	Adolescent Research Nurse	Centre for Adolescent Rheumatology Versus Arthritis, University College London	3rd Floor Central, 250 Euston Road, London, NW1 2PG
Dr	Avni Hindocha	Paediatric trainee	Royal Manchester Children's Hospital, Manchester University Hospitals NHS Trust,	Royal Manchester Children's Hospital, Manchester University Hospitals NHS Trust, Oxford Rd Manchester M13 9WL UK
Dr	John Ho	Consultant Paediatrician	Whipps Cross University Hospital, London	Whipps Cross Road, Leytonstone, London, E11 1NR
Mrs	Ruth Howman	Clinical Research Sister	Birmingham Children's Hospital, Birmingham Women's and Children's NHS Foundation Trust	Steelhouse Lane, Birmingham B4 6NH
Ms	Camilla Huber	Research & Development	Birmingham Women's Hospital, Birmingham Women's and Children's NHS Foundation Trust	Mindelsohn Way, Birmingham B15 2TG
Dr	Marjorie Illingworth	Paediatric Neurology Consultant	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Dr	Winnie Ip	Honorary Senior Lecturer & Consultant Paediatric Immunologist	Great Ormond Street Hospital for Children NHS Foundation Trust, Molecular and Cellular Immunology, University College London Great Ormond Street Institute of Child Health	Great Ormond Street, London WC1N 3JH, 30 Guilford Street, London, WC1N 1EH
Dr	Javed Iqbal	Consultant Paediatrician	East Lancs NHS Trust	Haslingden Road, Blackburn, BB2 3HH
Dr	Mark J Johnson	Consultant Neonatologist	Department of Neonatal Medicine, University Hospital Southampton NHS Foundation Trust, NIHR Biomedical Research Centre, University of Southampton	Tremona Road, Southampton, SO16 6YD
Dr	Christine E Jones	Consultant Paediatric Infectious Diseases	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Mr	James Jones	Paediatric Research Nurse	The Shrewsbury and Telford Hospital NHS Trust	Mytton Oak Road, Shrewsbury, Shropshire, SY3 8XQ
Dr	Jochen Kammermeier	Consultant Paediatric Gastroenterologist	Evelina London Children's Hospital	Westminster Bridge Road London SE1 7EH
Dr	Dagmar Kastner-Cole	Consultant Paediatrician	Tayside Children's Hospital, Ninewells Hospital and Medical School	Dundee, DD1 9SY,
Dr	Akhila Kavirayani	Consultant Paediatric Rheumatology	Oxford University Hospitals NHS Foundation Trust	Nuffield Orthopaedic Centre, Oxford, OX3 7HE
Prof	Deirdre Kelly	Consultant Paediatric Hepatologist	Liver Unit, Birmingham Women's & Children's NHS Foundation Trust, University of Birmingham	Steelhouse Lane, Birmingham B4 6NH, Edgbaston, Birmingham B15 2TT
Ms	Imogen Kelly	Clinical Nurse Specialist	Royal Hospital for Sick Children, Edinburgh	9 Sciennes Road, Edinburgh, EH1 9LF
Dr	Ciara Kennedy	Clinical Trials Coordinator	Great North Children's Hospital	Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP
Dr	Larissa Kerecuk	Clinical Research Specialty Lead Paediatrics, NIHR CRN	Birmingham Children's Hospital, Birmingham Women's and Children's NHS Foundation Trust	Steelhouse Lane, Birmingham B4 6NH

		West Midlands, Consultant Paediatric Nephrologist		
Mr	Charles Keys	Consultant Paediatric Surgery	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Miss	Aline Kimonyo	Research Coordinator	University College London Great Ormond Street Institute of Child Health	UCL Great Ormond Street Institute of Child Health 30 Guilford Street London WC1N 1EH
Mrs	Sharon King	Research Nurse	Great North Children's Hospital	Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP
Mrs	Vicky King	Clinical Trials Practitioner	Salisbury District Hospital	Salisbury, Wiltshire, SP2 8BJ
Dr	Fenella Kirkham	Paediatric Neurology Consultant	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Dr	Alice Leahy	Consultant Paediatric Rheumatologist	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton SO16 6YD
Ms	Gemma Lee	Clinical Nurse Specialist – Paediatric IBD	Evelina London Children's Hospital	Westminster Bridge Road London SE1 7EH
Dr	Julian Legg	Paediatric Respiratory Consultant	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Dr	Valentina Leone	Consultant Paediatric Rheumatology	Leeds Children Hospital	Leeds Teaching Hospital NHS Trust, Great George Street, LS1 3EX
Dr	Derek Lim	Consultant Clinical Geneticist	Clinical Genetics Department, West Midlands Regional Genetics Service, Birmingham Women's and Children's Hospital NHS Foundation Trust	Mindelsohn Way, Birmingham B15 2TG
Mrs	Adine Logan	Research Nurse	East Lancs NHS Trust	Haslingden Road, Blackburn, BB2 3HH
Prof	Jane Lucas	Professor of Paediatric Respiratory Medicine	PCD Centre, School of Clinical and Experimental Sciences, Faculty of Medicine and Institute for Life Sciences, University of Southampton, NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust;	Tremona Road, Southampton SO16 6YD
Dr	David Lynn	Consultant Paediatrician	NHS Forth Valley	Forth Valley Royal Hospital, Stirling Road, Larbert FK5 4WR
Mrs	Susan Macfarlane	Paediatric Research Nurse	Scottish Paediatric Research Network, Ninewells Hospital and Medical School	Dundee, DD1 9SY
Ms	Lydia Makusha	Neurology Specialist Nurse	Neurology Specialist Nurse, Neurology Department, Birmingham Children's Hospital, Birmingham Women's and Children's NHS Foundation Trust	Steelhouse Lane, Birmingham B4 6NH
Dr	Gulshan A Malik	Consultant Paediatrician	Royal Aberdeen Children hospital	Westburn road, Aberdeen Scotland, AB25 2ZG
Dr	Stephen D Marks	Reader and Consultant in Paediatric Nephrology	NIHR Great Ormond Street Hospital Biomedical Research Centre, University College London Great Ormond Street Institute of Child Health	30 Guilford Street, London WC1N 1EH
Dr	Verghese Mathew	Consultant Paediatrician	Hull University Teaching Hospitals NHS Trust	Anlaby Road, Hull, HU3 2JZ
Dr	Janet E McDonagh	Senior Lecturer in Paediatric and Adolescent Rheumatology	Versus Arthritis Centre for Epidemiology; Centre for MSK Research, University of Manchester; NIHR Biomedical Research Centre, Manchester University Hospital NHS Trust; Department of Paediatric and Adolescent Rheumatology, Royal Manchester Children's Hospital, Manchester University Hospitals NHS Trust	Centre for MSK Research, Stopford Building, University of Manchester Oxford Rd Manchester M13 9PT
Dr	Flora McErlane	Consultant Paediatric Rheumatologist and Associate Clinical Lecturer	Newcastle Hospitals NHS Foundation Trust and Institute of Health and Society, Newcastle University	Royal Victoria Hospital, Queen Victoria Road, Newcastle upon Tyne. NE1 4LP
Mrs	Ann McGovern	Senior Clinical Research Practitioner in Rheumatology	Royal Manchester Children's Hospital, Manchester University Hospitals NHS Trust,	Royal Manchester Children's Hospital, Manchester University Hospitals NHS Trust, Oxford Rd Manchester M13 9WL UK

Ms	Karen McIntyre	Paediatric Specialist Nurse	Ninewells Hospital and Medical School	Dundee, DD1 9SY
Dr	Ross McLean	Specialty Doctor in Paediatrics	NHS Lanarkshire	Kirklands, Fallside Road. Bothwell, G71 8BB
Dr	Paddy McMaster	Consultant in Paediatric Infectious Diseases	North Manchester General Hospital	Delauneys Road, Manchester, M8 5RB
Dr	Nabil Melhem	Consultant Paediatric Nephrologist	Department of Paediatric Nephrology, Evelina London Children's Hospital, Guy's & St. Thomas' Foundation Hospitals NHS Trust	Westminster Bridge Road, London, SE1 7EH, UK
Ms	Dawn Metcalfe	Clinical Trials Associate	Great North Children's Hospital	Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP
Ms	Danielle Miller	Children's Research Nurse	Oxford University Hospitals NHS Foundation Trust	John Radcliff hospital, WWLG1 room 10.15, Oxford, OX3 9DU
Ms	Lynne Mills	Information Analyst Advanced	NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Ms	Lisa Moyes	Paediatric Research Practitioner	Nottingham Children's Hospital, Queen's Medical Centre, Nottingham University Hospitals NHS Trust	Derby Road, Nottingham, NG72UH
Dr	Alasdair Munro	Clinical Research Fellow	NIHR Southampton Clinical Research Facility and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and Faculty of Medicine and Institute for Life Sciences, University of Southampton	Tremona Road, Southampton, SO16 6YD
Miss	Olivia Murphy-Parry	Paediatric Rheumatology Clinical Nurse Specialist	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton SO16 6YD
Dr	Mohamed Mutalib	Consultant paediatric gastroenterologist	Evelina London Children' Hospital	Westminster Bridge Road, London< SE1 7EH
Dr	Arvind Nagra	Consultant Paediatric Nephrologist	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton SO16 6YD
Dr	Sarveshni Naidoo	Consultant General Paediatrics	NHS Lanarkshire	Kirklands, Fallside Road. Bothwell, G71 8BB
Dr	Gary Nicolin	Consultant Paediatric Oncology	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Dr	Maggie Nyirenda	Consultant Paediatrician	University Hospital Lewisham	Paediatric Offices, Nockold House, University Hospital Lewisham, Lewisham High street, London, SE13 6LH
Mrs	Grainne O'Connor	Senior Paediatric Research Nurse	North Manchester General Hospital	Delauneys Road, Manchester, M8 5RB
Dr	Sian O'Riordan	Consultant Paediatric Immunology and Infectious Diseases	Leeds Children Hospital	Leeds Teaching Hospital NHS Trust, Great George Street, LS1 3EX
Dr	Briget Oates	Paediatric Consultant	University Hospital Crosshouse	Kilmarnock, KA2 0BE
Dr	Daniel Owens	Clinical Research Fellow	NIHR Southampton Clinical Research Facility and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and Faculty of Medicine and Institute for Life Sciences, University of Southampton	Tremona Road, Southampton, SO16 6YD
Ms	Krishna Panchal	Clinical Trials Support Officer	Research Department, Lancashire Teaching Hospitals NHS Trusts	Royal Preston Hospital, Sharoe Green Lane, Preston PR2 9HT
Ms	Sharon Parkes	Nephrology and Rare Disease Research Coordinator	Nephrology and Rare Disease Research Coordinator, R&D Department , Birmingham Women's and Children's NHS Foundation Trust	Steelhouse Lane, Birmingham B4 6NH
Mrs	Charlotte Passingham	Research Co-ordinator	Liver Unit, Birmingham Children's Hospital, Birmingham Women's and Children's NHS Foundation Trust	Steelhouse Lane, Birmingham B4 6NH
Mr	Ravin Patel	Medical Student	University of Southampton	University Rd, Southampton SO17 1BJ
Dr	Sanjay Patel	Consultant Paediatric Infectious Diseases	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD

Dr	Margaret Peebles	Consultant Paediatrician	Ninewells Hospital and Medical School	Dundee, DD1 9SY
Dr	Salina Persand	Clinical Research Practitioner	Imperial College Healthcare NHS Trust and Imperial College London. Children's Clinical Research Facility	
Mrs	Sharon Peters	Paediatric Infectious Diseases Nurse Specialist	North Manchester General Hospital	Delauneys Road, Manchester, M8 5RB
Mrs	Charlotte Phillips	Team leader	Childrens community Nursing Team, Kent community Health Foundation Trust	Trinity House, 110-112- Upper Pemberton, Kennington, Ashford, Kent, TN25 4AZ
Mrs	Helen Pidgeon	Clinical Trials Assistant	Salisbury District Hospital	Salisbury, Wiltshire, SP2 8BJ
Mrs	Sue Power	Paediatric Research Nurse	Poole Hospital NHS Foundation Trust	Longfleet Rd, Poole, BH15 2JB
Dr	Evgenia Preka	Consultant Paediatric Nephrologist	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton SO16 6YD
Ms	Vanessa Raimondo	Clinical Nurse Specialist	Royal Hospital for Sick Children, Edinburgh	9 Sciennes Road, Edinburgh, EH1 9LF
Dr	Jagadeesh Ramachandra	Consultant Paediatrician	Royal United Hospitals Bath NHS Foundation Trust	Combe Park, Bath, BA1 3NG
Dr	Ramya Ramanujachar	Consultant Paediatric Oncology	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Miss	Pernille Rasmussen	Clinical Nurse Specialist Nephrology	Department of Paediatric Nephrology, Evelina London Children's Hospital, Guy's & St. Thomas' Foundation Hospitals NHS Trust	Westminster Bridge Road, London, SE1 7EH, UK
Dr	Trevor Richens	Consultant Paediatric Cardiologist	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Dr	Valerie Rogers	Consultant Paediatric Rheumatologist	University Hospital Bristol NHS Foundation trust	Marlborough Street, Bristol, BS1 3NU
Dr	Erika Rojas-Jimenz	Paediatric Research Clinical Fellow	Poole Hospital NHS Foundation Trust	Longfleet Rd, Poole, BH15 2JB
Dr	Kevin Roman	Consultant Paediatric Cardiologist	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Ms	Chloe Saad	Clinical Research Assistant	University Hospital Lewisham	Paediatric Offices, Nockold House, University Hospital Lewisham, Lewisham High street, London, SE13 6LH
Mr	Stephen Saich	CRF Clinical Research Project Manager	NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Ms	Rebecca Sarjeant	Research Nurse	Great North Children's Hospital	Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP
Ms	Paula Saunderson	Clinical Trials Co-ordinator	Alder Hey Children's NHS Foundation Trust	Eaton Road, West Derby, Liverpool, L12 2AP
Miss	Francesca Schiavone	Clinical Nurse Specialist, Paediatric Gastroenterology	Morriston Hospital, Swansea Bay University Health Board	Swansea, SA6 6NL
Ms	Beatrice Selby	Clinical research coordinator	NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton SO16 6YD
Dr	Fiona Shackley	Consultant Paediatric Infectious Diseases	Sheffield Children's Hospital	Clarkson St, Broomhall, Sheffield S10 2TH
Ms	Jennifer Sharp	Research Nurse	Paediatric Research , Cambridge University Hospitals NHS Foundation Trust	Hills Road, Cambridge, CB2 0QQ
Dr	Meera Shaunak	Clinical Research Fellow	NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Dr	Mohan Shenoy	Consultant Paediatric nephrologist	Royal Manchester Children's Hospital, Manchester University Hospitals NHS Trust,	Royal Manchester Children's Hospital, Manchester University Hospitals NHS Trust, Oxford Rd Manchester M13 9WL UK
Dr	Vinay Shivamurthy	Consultant Paediatric Rheumatology	Evelina London Children's Hospital	Westminster Bridge Road London SE1 7EH
Ms	Theresa Simangan	Senior Paediatric Research Nurse	Whipps Cross University Hospital, London	Whipps Cross Road, Leytonstone, London, E11 1NR

Dr	Jaspal Singh	Paediatric Neurology Consultant	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Mrs	Samantha Small	Paediatric Rheumatology Clinical Nurse Specialist	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton SO16 6YD
Dr	Ameenat Lola Solebo	Consultant Paediatric Ophthalmology	Great Ormond Street Hospital for Children NHS Foundation Trust, Population, Policy & Practice Research & Teaching Department, University College London Great Ormond Street Institute of Child Health	Great Ormond Street, London WC1N 3JH, 30 Guilford Street, London WC1N 1EH
Dr	Helen Spencer	Consultant in Transplant and Respiratory Medicine	Great Ormond Street Hospital for Children NHS Foundation Trust	Great Ormond Street, London WC1N 3JH
Dr	Isaac Staff	Foundation Doctor	James Paget University Hospital	Lowestoft Rd, Gorleston, NR31 6LA
Dr	Karnam Sugumar	Consultant Paediatrician	Department of Child Health, Lancashire Teaching Hospitals NHS Trusts	Royal Preston Hospital, Sharoe Green Lane, Preston PR2 9HT
Ms	Zoe Swash	Clinical research coordinator	NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Dr	Sneha Tandon	Consultant Paediatric Haematologist	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton SO16 6YD
Dr	Marc Tebruegge	Consultant in infectious diseases and immunology	Evelina London Children's Hospital	Westminster Bridge Road London SE1 7EH
Ms	Evelyn Thomson	Research Nurse	Great North Children's Hospital	Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP
Dr	Mark Tighe	Consultant Paediatrician	Poole Hospital NHS Foundation Trust	Longfleet Rd, Poole, BH15 2JB
Mrs	Joanne Tomlinson	Research Nurse	University Hospitals of North Midlands NHS Trust	Staffordshire Children's Hospital at Royal Stoke, Newcastle Road, Stoke on Trent, ST4 6QG
Dr	Nicola Trevelyan	Consultant Paediatric Diabetologist	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Dr	Brigitte Vollmer	Paediatric Neurology Consultant	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Dr	Woolf Walker	Paediatric Respiratory Consultant	PCD Centre, University Hospital Southampton NHS Foundation Trust, School of Clinical and Experimental Sciences, Faculty of Medicine and Institute for Life Sciences, University of Southampton, NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton SO16 6YD
Dr	Jo Walsh	Consultant Paediatric Rheumatology	Royal Hospital for Children Glasgow	345 Govan Rd, Glasgow G51 4TF
Ms	Rachel Wane	Lead Research Nurse – Children's Team	Bradford Teaching Hospitals NHS Foundation Trust	Duckworth Lane, Bradford, West Yorkshire, BD9 6RJ
Dr	Evangeline Wassmer	Paediatric Neurology Consultant	Neurology Dept, Birmingham Children's Hospital, Birmingham Women's and Children's NHS Foundation Trust	Steelhouse Lane, Birmingham B4 6NH
Mrs	Elizabeth Waxman	Paediatric Research Nurse Manager	Glasgow Clinical Research Facility	345 Govan Rd, Glasgow G51 4TF
Prof	Lucy R Wedderburn	Consultant Paediatric Rheumatology	Infection, Immunity and Inflammation Research & Teaching Department, University College London Great Ormond Street Institute of Child Health, Paediatric Rheumatology, Great Ormond Street Hospital NHS Foundation Trust, NIHR Great Ormond Street Hospital Biomedical Research Centre, Arthritis Research UK Centre for Adolescent Rheumatology, GOS Institute of Child Health, University College London	30 Guilford Street, London, WC1N 1EH, Great Ormond Street, London WC1N 3JH
Mrs	Lucy Wellings	Paediatric and Adolescent Research Nurse	University College London NHS Foundation Trust	3rd Floor Central, 250 Euston Road, London, NW1 2PG

Dr	Andrea Whitney	Paediatric Neurology Consultant	University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton, SO16 6YD
Dr	Elizabeth Whittaker	Consultant Paediatric Infectious Diseases	Imperial College Healthcare NHS Trust and Imperial College London. Children's Clinical Research Facility	2nd Floor Cambridge Wing, Norfolk Place, London W2 1NY
Mrs	Rachel Wiffen	Paediatric Research Practitioner	Nottingham Children's Hospital, Queen's Medical Centre, Nottingham University Hospitals NHS Trust	Derby Road, Nottingham, NG72UH
Mr	Matthew Wilkins	Clinical research coordinator	NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust	Tremona Road, Southampton SO16 6YD
Ms	Jessica Williams	Data Manager	Great North Children's Hospital	Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP
Dr	Mark Wood	Consultant Paediatric Rheumatology	Leeds Children Hospital	Leeds Teaching Hospital NHS Trust, Great George Street, LS1 3EX
Mrs	Sophie Wool	Research Nurse	Paediatric Oncology and Haematology, Cambridge University Hospitals NHS Foundation Trust	Hills Road, Cambridge, CB2 0QQ
Ms	Suzannah Wright	Project Manager	Paediatric Infectious Diseases Research Group, St George's, University of London	Cranmer Terrace, London, SW17 0RE
Mrs	Wing Han Wu	Clinical Research Coordinator	Centre for Adolescent Rheumatology Versus Arthritis, University College London	3rd Floor Central, 250 Euston Road, London, NW1 2PG
Ms	Caroline Youle	Respiratory Nurse Specialist/ Research Nurse	Nottingham Children's Hospital, Queen's Medical Centre, Nottingham University Hospitals NHS Trust	Derby Road, Nottingham, NG72UH

Appendix B: Participating Centres

Participating centre	Number of Patients Recruited	%
University Hospital Southampton	163	10.99
John Radcliffe Hospital Oxford	26	1.75
Royal Manchester Children's Hospital	89	6.00
Birmingham Women's and Children's Hospital	145	9.78
Cardiff and Vale University Health Board	35	2.36
Nottingham Children's Hospital	47	3.17
Great North Children's Hospital	169	11.40
Leeds General Infirmary Children's Hospital	18	1.21
Bradford Teaching Hospital	12	0.81
Alder Hey Children's Hospital Liverpool	42	2.83
Great Ormond Street Hospital	176	11.87
St Georges Hospital London	30	2.02
Sheffield Children's Hospital	56	3.78
Royal Hospital for Children Glasgow	57	3.84
Royal Hospital for Sick Children Edinburgh	18	1.21
University Hospital Coventry and Warwickshire	23	1.55
East Lancashire Hospitals NHS Trust	35	2.36
Northern Manchester General Hospital	4	0.27
Addenbrooke's Hospital Cambridge	49	3.30
Swansea Bay University Health Board	2	0.13
Ayrshire and Arran Health Board	4	0.27
Norfolk and Norwich University Hospital	2	0.13
Salisbury NHS Trust	6	0.40
University College London Hospitals	5	0.34
James Paget University Hospital	23	1.55
Kent Community Health	10	0.67
Royal Marsden Trust	6	0.40
Bristol Royal Hospital for Children	21	1.42
Royal Alexandra Children's Hospital Brighton	13	0.88
Tayside Children's Hospital	15	1.01
Royal Aberdeen Children's Hospital	25	1.69
NHS Forth Valley	2	0.13
Royal United Hospitals Bath	16	1.08
Evelina London Children's Hospital	28	1.89
NHS Lanarkshire	47	3.17
University Hospital North Midlands	11	0.74
St Marys Hospital London	3	0.20
Lancashire Teaching Hospital	2	0.13
Kings College Hospital	22	1.48
Poole Hospital	23	1.55
Barts Health NHS Trust	3	0.20

Appendix C: Weekly Questionnaire

In the week beginning xx/xx/xxxx have you experienced any of the following symptoms?		
1.1	I have had no symptoms	○ I have had no symptoms ○ I have had symptoms
1.2	Measured temperature above 38 °C	○ Yes ○ No
1.2.1	**If 'Measured temperature above 38 °C' is equal to 'Yes' answer this question:** Which days did you measure a temperature above 38 °C?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.2.2	**If 'Measured temperature above 38 °C' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.3	Cough	○ Yes ○ No
1.3.1	**If 'Cough' is equal to 'Yes' answer this question:** Which days did you experience a cough?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.3.2	**If 'Cough' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.4	Shortness of breath	○ Yes ○ No
1.4.1	**If 'Shortness of breath' is equal to 'Yes' answer this question:** Which days did you experience shortness of breath?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday

		☐ Sunday
1.4.2	**If 'Shortness of breath' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.5	Sore throat	○ Yes ○ No
1.5.1	**If 'Sore throat' is equal to 'Yes' answer this question:** Which days did you experience sore throat?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.5.2	**If 'Sore throat' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.6	Blocked nose	○ Yes ○ No
1.6.1	**If 'Blocked nose' is equal to 'Yes' answer this question:** Which days did you experience blocked nose?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.6.2	**If 'Blocked nose' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.7	Red eyes	○ Yes ○ No
1.7.1	**If 'Red eyes' is equal to 'Yes' answer this question:** Which days did you experience red eyes?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.7.2	**If 'Red eyes' is equal to 'Yes' answer this question:**	○ Yes ○ No

	Have you experienced a worsening of the above symptom?	
1.8	Headache	○ Yes ○ No
1.8.1	**If 'Headache' is equal to 'Yes' answer this question:** Which days did you experience headache?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.8.2	**If 'Headache' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.9	Joint pain	○ Yes ○ No
1.9.1	**If 'Joint pain' is equal to 'Yes' answer this question:** Which days did you experience joint pain?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.9.2	**If 'Joint pain' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.10	Muscle pain	○ Yes ○ No
1.10.1	**If 'Muscle pain' is equal to 'Yes' answer this question:** Which days did you experience muscle pain?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.10.2	**If 'Muscle pain' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.11	Fatigue	○ Yes ○ No

1.11.1	**If 'Fatigue' is equal to 'Yes' answer this question:** Which days did you experience fatigue?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.11.2	**If 'Fatigue' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.12	Chills	○ Yes ○ No
1.12.1	**If 'Chills' is equal to 'Yes' answer this question:** Which days did you experience chills?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.12.2	**If 'Chills' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.13	Nausea	○ Yes ○ No
1.13.1	**If 'Nausea' is equal to 'Yes' answer this question:** Which days did you experience nausea?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.13.2	**If 'Nausea' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.14	Vomiting	○ Yes ○ No
1.14.1	**If 'Vomiting' is equal to 'Yes' answer this question:** Which days did you experience vomiting?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday

		☐ Saturday ☐ Sunday
1.14.2	**If 'Vomiting' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.15	Diarrhoea	○ Yes ○ No
1.15.1	**If 'Diarrhoea' is equal to 'Yes' answer this question:** Which days did you experience diarrhoea?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.15.2	**If 'Diarrhoea' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.16	Loss of smell or taste	○ Yes ○ No
1.16.1	**If 'Loss of smell or taste' is equal to 'Yes' answer this question:** Which days did you experience loss of smell or taste?	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday
1.16.2	**If 'Loss of smell or taste' is equal to 'Yes' answer this question:** Have you experienced a worsening of the above symptom?	○ Yes ○ No
1.17	Other symptoms	
2.1	Has your child changed medication this week?	○ Yes ○ No
2.1.1	**If 'Has your child changed medication this week?" if equal to 'Yes' answer this question:** What medication has changed and how?	

2.2	Was your child in contact with someone who is diagnosed with or suspected to have coronavirus?	○ Yes ○ No ○ Not known
2.3	Did your child visit the NHS because you were worried about coronavirus infection?	○ Yes ○ No ○ Not known
2.4	Did your child have a test for coronavirus?	○ Yes ○ No ○ Not known
2.5	Did your child have a confirmed diagnosis of coronavirus infection?	○ Yes ○ No ○ Not known
2.6	Was your child admitted to hospital because of a coronavirus infection?	○ Yes ○ No ○ Not known
2.6.1	**If 'Was your child admitted to hospital because of a coronavirus infection?' is equal to 'Yes' answer this question**: When was your child admitted?	dd-mm-yyyy
2.6.2	**If 'Was your child admitted to hospital because of a coronavirus infection?' is equal to 'Yes' answer this question:** How many days was your child admitted?	
2.7	Did you have to self-isolate your child because they had symptoms or because of medical advice related to coronavirus?	○ Yes ○ No ○ Not known
2.7.1	**If 'Did you have to self-isolate your child because they had symptoms or because of medical advice related to coronavirus?' is equal to 'Yes' answer this question:** How many days did you self-isolate your child this week?	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7
2.8	Were immunosuppressive drugs postponed because of coronavirus infection?	○ Yes ○ No ○ Not known
2.8.1	**If 'Were immunosuppressive drugs postponed because of coronavirus infection?' is equal to 'Yes' answer this question**: How many days did you	☐ 1 ☐ 2 ☐ 3 ☐ 4

	postpone the immunosuppressants this week?	☐ 5 ☐ 6 ☐ 7
2.9	Did your child miss any sports or fun activities because of the coronavirus pandemic?	○ Yes ○ No ○ Not known
2.9.1	**If 'Did your child miss any sports or fun activities because of the coronavirus pandemic?' is equal to Yes answer this question:** How many activities did your child miss?	
2.10	Did your child miss school because of coronavirus infection?	○ Yes ○ No ○ Not known
2.10.1	**If 'Did your child miss school because of coronavirus infection?' is equal to Yes answer this question:** How many days of school did your child miss this week?	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7
2.11	On a scale of 0-10, how worried are you about coronavirus affecting your child? (0 = not worried, 10 = extremely worried)	
2.12	Is there anything that you are particularly worried about that you would like to share?	

Appendix D:

Symptom frequency by primary diagnosis

Symptoms	JIA (%)	Other rheumatology diagnosis (%)	Airways disease (%)	Immunodeficiency disorder (%)	Diabetes (%)	Solid organ or bone marrow transplant (%)	Nephrotic syndrome (%)	Other kidney disease (%)	IBD (%)	Other gastroenterology and hepatology (%)	Malignant haematology & oncology (%)	Neurology (%)	Other (%)
Fever	1.63	0.81	0.24	0.73	0.16	0.41	0.08	0.08	0.00	0.08	0.57	0.24	0.33
Cough	4.80	1.54	1.63	1.54	0.24	1.46	0.57	0.16	0.08	0.00	0.89	0.16	0.65
SOB	1.63	0.89	0.65	0.65	0.08	0.08	0.16	0.08	0.16	0.08	0.16	0.08	0.81
Sore throat	6.02	2.28	0.98	0.98	0.16	0.41	0.24	0.24	0.49	0.33	0.89	0.33	0.89
Blocked nose	7.48	2.60	1.79	1.30	0.49	1.30	0.65	0.41	0.73	0.33	0.57	0.24	1.22
Red eyes	4.07	2.11	0.57	1.14	0.49	0.41	0.49	0.08	0.33	0.08	0.57	0.16	0.57
Headache	11.30	4.96	1.30	2.20	0.98	1.54	0.65	0.33	0.98	0.49	1.87	0.73	1.63
Vomiting	3.66	0.89	0.33	0.65	0.08	0.89	0.24	0.24	0.00	0.16	1.14	0.08	0.98
Diarrhoea	4.23	1.63	0.57	1.46	0.49	0.81	0.33	0.33	0.81	0.16	0.73	0.24	0.73
Joint pain	19.84	3.98	0.24	1.22	0.16	1.30	0.65	0.24	0.81	0.08	1.87	0.41	1.06
Muscle pain	8.46	3.33	0.57	1.22	0.33	1.06	0.65	0.24	0.49	0.24	1.38	0.33	0.81
Fatigue	13.98	4.07	1.30	2.60	0.49	1.30	0.89	0.57	1.30	0.41	3.25	0.89	1.30
Chills	2.11	1.06	0.08	0.49	0.08	0.41	0.08	0.08	0.24	0.08	0.33	0.33	0.24

Abbreviations: SOB shortness of breath, JIA juvenile idiopathic arthritis, IBD inflammatory bowel disease

Symptom frequency by medication

Symptoms	Methotrexate (%)	Hydroxychloroquine (%)	Other DMARDs (%)	Corticosteroids (%)	Anti-TNF therapy (%)	Tocilizumab (%)	Other biologic drugs (%)	MMF (%)
Fever	4.92	9.09	0.92	5.62	4.62	4.08	11.11	5.34
Cough	12.44	14.55	9.17	14.06	15.84	4.08	8.33	15.27
SOB	3.11	3.64	1.83	6.02	4.29	8.16	5.56	4.58
Sore throat	16.06	21.82	18.35	11.24	18.15	18.37	8.33	10.69
Blocked nose	19.69	25.45	13.76	13.65	23.76	14.29	19.44	17.56
Red eyes	12.69	10.91	8.26	10.44	11.55	14.29	13.89	6.11
Headache	29.27	45.45	29.36	28.11	30.69	28.57	27.78	25.19
Vomiting	12.18	9.09	4.59	12.05	8.25	12.24	8.33	7.63
Diarrhoea	9.84	10.91	11.93	11.65	11.88	20.41	8.33	12.98
Joint pain	43.78	43.64	33.03	26.91	46.20	69.39	36.11	22.14
Muscle pain	20.98	41.82	22.02	24.50	21.45	30.61	25.00	19.08
Fatigue	39.12	43.64	29.36	34.14	34.65	40.82	38.89	24.43
Chills	5.44	12.73	5.50	7.23	6.93	6.12	5.56	6.87
Nausea	31.09	27.27	15.60	20.88	25.41	26.53	16.67	15.27
Loss of smell	0.52	1.82	0.00	0.80	0.33	0.00	0.00	1.53

Abbreviations: DMARDs disease modifying anti-rheumatic drugs, MMF mycophenolate mofetil

Symptoms	Chemotherapy (%)	Azathioprine (%)	Other antibiotics and antivirals (%)	Tacrolimus (%)	Inhalers (%)	Insulin (%)	NSAIDs (%)	IV or SC IG (%)
Fever	10.29	7.35	7.14	3.80	8.14	3.66	9.72	2.63
Cough	14.71	25.00	18.45	15.19	31.40	8.54	15.28	13.16
SOB	5.88	8.82	5.95	3.16	16.28	3.66	8.33	7.89
Sore throat	8.82	13.24	10.71	6.96	18.60	7.32	13.89	0.00
Blocked nose	10.29	16.18	13.69	14.56	36.05	9.76	25.00	10.53
Red eyes	10.29	8.82	9.52	5.70	15.12	9.76	16.67	5.26
Headache	27.94	32.35	20.83	18.35	32.56	25.61	44.44	15.79
Vomiting	22.06	10.29	14.29	8.86	12.79	7.32	9.72	5.26
Diarrhoea	14.71	10.29	13.10	10.13	12.79	10.98	12.50	5.26
Joint pain	29.41	14.71	20.24	17.09	18.60	8.54	61.11	18.42
Muscle pain	23.53	11.76	17.26	14.56	19.77	7.32	31.94	7.89
Fatigue	47.06	30.88	30.36	18.35	30.23	17.07	54.17	18.42
Chills	7.35	2.94	4.17	3.80	6.98	1.22	11.11	0.00
Nausea	30.88	19.12	17.86	12.66	20.93	10.98	27.78	10.53
Loss of smell	0.00	0.00	0.00	1.27	1.16	0.00	4.17	0.00

Abbreviations: NSAIDs non-steroid anti-inflammatory drugs, IV intravenous, SC subcutaneous, IG immunoglobulin

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	4-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-6
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	6-8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.