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Long Covid and the mental and physical health of children and young people; a national matched cohort study (CLoCk).

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Abstract

Introduction: There is uncertainty surrounding the diagnosis, prevalence, phenotype, duration and treatment of Long COVID. This study aims to (a) describe the clinical phenotype of post-COVID symptomatology in CYP with laboratory-confirmed SARS-CoV-2 infection compared to test-negative controls (b) produce an operational definition of Long COVID in CYP (c) establish the prevalence of Long COVID in CYP.

Methods and analysis: A cohort study of SARS-CoV-2 positive CYP aged 11-17 years compared with age-, sex- and geographically-matched SARS-CoV-2 test-negative CYP. CYP aged 11-17 testing positive and negative for SARS-CoV-2 infection will be identified and contacted 3, 6, 12 and 24 months after the test date. Consenting CYP will complete an online questionnaire. We will recruit 3,000 test positives and 3,000 test negatives. Data visualisation techniques will be used to examine trajectories over time for symptoms and variables measured repeatedly, separately by original test status. Summary measures of fatigue and mental health dimensions will be generated using dimension reduction methods such as latent variables/latent class/PCA methods. Cross-tabulation of collected and derived variables against test status and discriminant analysis will help operationalise preliminary definitions of Long COVID.

Ethics and Dissemination: Research Ethics Committee Approval granted. Data will be stored in secure PHE servers or UCL's Data Safe Haven. Risks of harm will be minimised by providing information on where to seek support. Results will be published on a pre-print server followed by journal publication, with reuse of articles under a CC BY licence. Data will be published with protection against identification when small frequencies.

Study registration: Study registered with ISRCTN: Trial ID: ISRCTN34804192 and granted Urgent Public Health prioritisation.

Data Sharing: Applications for relevant anonymised data should be submitted to the Public Health England office for Data Release: <https://www.gov.uk/government/publications/accessing-public-health-england-data/about-the-phe-odr-and-accessing-data>

Article Summary

STRENGTHS

- This study does not start with an arbitrary definition of a new condition – ‘opinion based medicine’
- Rather it represents ‘evidence based medicine’ - we will seek the views of 6,000 children and young people on what they have experienced physically and mentally in the months following COVID-19
- The study incorporates a comparator matched cohort of children and young people who have experienced a pandemic, school closure and social isolation but who had a negative COVID test

WEAKNESSES

- The comparator matched cohort of children and young people must also have had a reason to seek a COVID test: symptoms, anxiety, a contact or a bereavement
- Ideally, we would test all children for antibodies to confirm COVID-19 positive and negative status throughout the study period but we thought would significantly reduce participation

Introduction

Currently, there is huge uncertainty surrounding the diagnosis, prevalence, phenotype, duration and treatment of Long COVID. There is currently no diagnostic test or code for Long COVID. Consequently, cases of Long COVID are not captured in routine National Health Service (NHS) administrative datasets. Instead, Long COVID may be coded as a variety of different conditions in hospital or symptom clusters in non-hospitalised CYP. However, it is possible the symptoms associated with Long COVID are in fact a mixture of factors relating to the pandemic and lockdown as a whole rather than the viral infection itself. For example, factors such as social isolation, anxiety, depression or educational concerns may be the root cause of these symptoms in CYP both with and without SARS-CoV-2 infection. The effects on the developing brain and behaviour of adolescents could be far reaching¹.

Despite acute COVID-19 illness being milder in CYP, it should not be assumed that those CYP at low risk of life-threatening acute infections^{2,3} do not suffer the longer-term consequences of SARS-CoV-2 infection. It is important to study Long COVID within this population given that the psychological and social impact of Long COVID could have major consequences for transition to adulthood. There is a clear need to define the clinical phenotype of Long COVID in order to understand those most at risk, the illness trajectory and to provide accurate information on the natural course of the condition. It is equally important to understand both the physical and mental health impact on CYP with Long COVID, given the rise in mental health problems among CYP since the start of the pandemic⁴. Obtaining a better understanding of which CYP are affected will help with targeting potential interventions.

The greatest risk factor for severe acute SAR-CoV-2 illness has been old age, with other risk factors at all ages including obesity, comorbid long-term conditions, learning and neurological disabilities, mental health problems and ethnic minority status. It is plausible that such CYP may be most at risk of suffering from Long COVID, given that much is still unknown in CYP about the immunological susceptibility and underlying biology of Long COVID. Of all CYP, those likely to be most at risk of Long COVID are teenagers, with existing literature showing they make up the majority of CYP with chronic fatigue, post viral syndromes and persistent symptoms⁵.

In adults, there is emerging evidence that gender is a risk factor for Long COVID, with middle-aged females more susceptible than men⁶. In terms of symptoms, two main groupings have been identified (i) respiratory symptoms (e.g. cough, shortness of breath) as well as fatigue and headaches, and (ii) multi-system, including the brain, gut and heart. Among adults with Long COVID, heart symptoms such as palpitations or fast heartbeat, pins and needles or numbness and problems concentrating ('brain fog') have been reported. Experiencing a greater number of symptoms during the first week of infection, as well as older age, have also been linked to Long COVID. It should be noted mental health conditions were not reported in this cohort. Four syndromes have been described in adults: Post-viral fatigue; Fluctuating multi-system symptoms; Post-intensive care syndrome; and Lasting organ damage. It is known in both adults and young people that a wide range of long-term physical conditions increase the risk of mental ill-health, particularly if the condition involves the central nervous system, with several studies

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3 reporting increased rates of all common mental health conditions in children⁷. Moreover, fatigue
4 has also been studied in paediatric long-term conditions including CYP with multiple sclerosis^{8,9}.
5 Emerging clinical observations and preliminary research indicate that COVID-19 can have a
6 long-term impact on CYP in a range of domains^{10,11} but well conducted, methodologically robust
7 studies are lacking.
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10 This study primarily aims to (a) describe the clinical phenotype and prevalence of post-COVID
11 symptoms (e.g. pain or physical symptoms, fatigue, sleep problems, mental health problems)
12 among test positive and test negative CYP, (b) produce an operational definition of Long COVID
13 in CYP, and (c) establish the prevalence of Long COVID in CYP testing positive for SARS-CoV-
14 2 infection. The second aim is of particular importance given that this is a prerequisite for any
15 future epidemiological or interventional study. This will be achieved by using the empirical data
16 we will acquire from 6,000 CYP and a national Delphi consensus process.
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20 **Methods**

21 *Study design and setting*

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25 Public Health England (PHE) has been conducting national surveillance of SARS-CoV-2 since
26 the start of the pandemic in England. PHE receives daily electronic notifications of all SARS-
27 CoV-2 RT-PCR tests performed in healthcare settings (Pillar 1 tests) and in the community
28 (Pillar 2 tests), which are reported through the Second Generation Surveillance System (SGSS).
29 Information within the SGSS reports includes NHS number, name, age, sex, postcode, date of
30 sample, reporting laboratory and test result. PHE also has access to the electronic Patient
31 Demographic Service (PDS), which contains the names, addresses and status (alive/dead) of
32 all patients registered with the NHS.
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36 A sample of CYP aged 11-17 years old when testing positive for SARS-CoV-2 between
37 September 2020 and March 2021 and twice as many COVID test-negative CYP matched for
38 age, sex and region identified through SGSS will be linked to PDS using available identifiers
39 and postal addresses. A letter will be posted to them, informing them about the study and
40 inviting them to take part using an online link. This link will provide them with information about
41 the study, with an option to consent online and complete a short recruitment questionnaire (or
42 both as paper options).
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46 This will be a cohort study of SARS-CoV-2 test-positive CYP aged 11-17 years matched on the
47 test date, age, sex and geography to SARS-CoV-2 test-negative controls identified by PHE.
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49 *Participants*

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52 Between 1st September 2020 and 31st March 2021, 234,803 CYP aged between 11 and 17 years
53 were tested positive for SARS-CoV-2 in England, and 1,245,288 CYP tested negative. Among
54 those who tested negative, 80,365 were excluded as they had a positive result pre- and/or post
55 their negative test and we wish to compare test-positive with test-negative CYP. The positive and
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3 negative cohorts were matched using age at test, gender, month of test, and lower super output
4 area resulting in 102,402 positive individuals and 147,561 negative individuals. Matched
5 individuals were checked against PDS to exclude any individuals who have died, and to extract
6 participants addresses to send invitation letters. 33 individuals were excluded because of death
7 since their COVID-19 test (6 among those positive and 27 among those negative), and 11,982
8 individuals of the positive cohort and 16,635 individuals of the negative cohort were excluded as
9 an address was not available. Finally, 246 CYP were excluded as they were included in a previous
10 pilot study which helped inform our methodology. Following exclusions, 90,227 positive CYP and
11 130,243 negative CYP form the population from which we will randomly sampled individuals for
12 inclusion within the study.
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16 Participants will be contacted in a ratio of 1:2 positives:negatives on the expectation of a lower
17 participation rate in the latter. We anticipate 20% to be recruited in the positive group, as
18 estimated by CYP recruitment rates in other PHE studies on COVID-19 (sKIDs)¹². We also
19 oversampled CYP who had a test in the months of January-March 2021 because only for these
20 groups we will collect information at 3 months of follow-up.
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24 This is shown schematically in Figure 1.
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26 *Data collection*

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28 Participating families of CYP will be contacted 3, 6, 12 and 24 months after the CYP's SARS-
29 CoV-2 test (depending on recruitment month) and invited to take part in the study. Following
30 online informed consent, the CYP will self-complete an online (or paper) questionnaire about
31 their mental and physical health. CYP towards the lower end of the 11-18 age band and CYP
32 with special educational needs or disability may require the help of a carer to complete the
33 questionnaire.
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37 *Outcomes*

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39 The questionnaires given to CYP include elements of the ISARIC Paediatric COVID-19 follow-
40 up questionnaire¹³ and the recent Mental Health of Children and Young people in England
41 surveys¹⁴ to facilitate international comparisons regarding the risk factors and profile of Long
42 COVID in CYP. The questionnaires given to CYP were designed together with the International
43 Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Paediatric Working
44 Group to produce a harmonised data collection tool, allowing for standardisation and
45 metanalysis by design.
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49 The elements taken from the ISARIC Paediatric COVID-19 follow-up questionnaire¹³ include
50 questions about demographics and physical symptoms, with particular questions enquiring
51 about cough and fever, given that these are the main acute symptoms in non-hospitalised
52 CYP¹⁵ and gastrointestinal symptoms, as a study has shown such symptoms were common in
53 seropositive CYP¹⁶. It is likely other symptoms will manifest later in Long COVID (e.g., tiredness,
54 headaches, myalgia etc.), with the skin rashes and cardiac problems in hospitalised children
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3 with Paediatric multisystem inflammatory syndrome being borne in mind for Long COVID⁵.
4 Those older CYP could very well overlap with adult symptomatology (e.g., a neuropsychiatric-
5 encephalitic sub-group).
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8 In terms of the other questions, the Strengths and Difficulties Questionnaire (SDQ)¹⁷ will be
9 used to assess emotional and mental health, consisting of 25 items. The EQ-5D-Y¹⁸ will be used
10 as a measure of quality of life/functioning, with fatigue measured using the 11-item Chalder
11 Fatigue Questionnaire (CFQ)¹⁹. Additionally, the short, 7-item version of The Warwick
12 Edinburgh Mental Wellbeing Scale (WEMWBS)²⁰ will be included. Loneliness will be measured
13 using the 4-item UCLA Loneliness Scale for Children²¹ as well as self-reported school
14 attendance.
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18 The length of the online self-assessment has an estimated completion time of approximately 20
19 minutes for CYP. The CYP do not have to complete all of the questions at once but can pause
20 and save the answers at any point.
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22 *Statistical analyses*

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25 Response rates for positive and negative CYP will inform expectations of final study size and
26 possibly refinement of the sampling percentages. Descriptive statistics will be used for all
27 dimensions collected at baseline and the follow-up questionnaires, separately by test status,
28 wave and month of test. Appropriate data visualisation techniques will be used to examine
29 trajectories over time for those variables that are measured repeatedly, separately by test status
30 and month of test. Summary measures of the fatigue and mental health dimensions will be
31 generated using dimension reduction methods such as latent variables/latent class/PCA
32 methods. Cross-tabulation of latent variables against test status as well as discriminant analysis
33 will help operationalise preliminary definitions of Long COVID. These will be compared with
34 definitions based on categorisation of prolonged symptoms supplemented by a Delphi
35 consensus process.
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39 *Sample size*

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42 A total of 5,000 participants (2,500 test-positive and 2,500 test-negative) would give 80% power
43 to detect at least a 4% difference in symptoms at 5% significance, if the COVID-19 negative
44 participants had a prevalence similar to that reported for adults (i.e., 34%). Greater baseline
45 prevalences (e.g., 40%) would require slightly greater numbers for the same power and
46 confidence; smaller baseline prevalences (e.g., 20%) smaller numbers. However, identifying risk
47 factors for long COVID-19 would require studying demographic, social, family and clinical data
48 and thus we would require larger numbers. For this reason, we are targeting the recruitment of
49 6,000 participants.
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Patient and Public Involvement

Resources have been allocated for any Patient and Public Involvement (PPI) activities at INVOLVE rates including a nationally representative PPI research advisory group. PPI members will be offered training and support in accordance with the INVOLVE²² report and other guidance²³ including online training. PPI meetings will take place quarterly.

Ethics and Dissemination

Ethical considerations

PHE has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for national surveillance of communicable diseases. Individual patient consent is not required for initial invitation to the study. Parents/carers and young people will be sent an invitation with a link to the website with the relevant information sheets and consent forms. They will have the opportunity to ask any questions about the study. Parents/carers of CYP under 16 years of age will be asked to complete a Parent/carer consent form. The young person will also be asked to sign an assent form to indicate their agreement. 16-18-year-olds will be asked for consent (using the Young Person Consent Form); but their parents will not. This is in line with HRA recommended processes²⁴.

Study approved by Yorkshire & The Humber - South Yorkshire Research Ethics Committee (REC reference: 21/YH/0060; IRAS project ID:293495).

It is possible that the questionnaires may make some vulnerable participants feel fatigued or distressed from completing questionnaires relating to their mental health and/or report serious symptoms that put them at immediate risk. The research team will provide information on where to seek support and provide self-help information. Unfortunately, the researchers are unable to provide medical advice. However, existing national surveys of children's mental health also follow this risk protocol.

Dissemination

Peer reviewed publications, briefings for policy makers and lay summaries for participants and CYP and carers. Results will be made public, initially on a pre-print server and we will allow reuse of articles under a CC BY licence. The dataset will be made publicly available.

Author contributions:

Terence Stephenson t.stephenson@ucl.ac.uk conceived the idea for the study, submitted the successful grant application and undertook the first revision of the manuscript.

Roz Shafran r.shafran@ucl.ac.uk provided ideas on mental health follow up to the original grant application, submitted the ethics and R&D applications and revised the manuscript.

Bianca De Stavola b.destavola@ucl.ac.uk provided statistical input to the design and analysis, including sample size calculations.

Natalia Rojas n.rojas@ucl.ac.uk wrote the first draft of the manuscript based on the grant application, protocol and ethics form and compiled the references.

Felicity Aiano Felicity.Aiano@phe.gov.uk helped develop the study design

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Kelsey McOwat Kelsey.Mcowat@phe.gov.uk adapted the questionnaire for the online SNAP survey platform.

Maria Zavala Maria.Zavala@phe.gov.uk undertook a separate pilot study which informed the CLoCk consent process and the online questionnaire.

Ruth Simmons Ruth.Simmons@phe.gov.uk designed the participant sampling and dataflow.

Shamez Ladhani shamez.ladhani@phe.gov.uk operationalised the regulatory and recruitment ideas for the study and revised the manuscript.

Olivia Swann and Elizabeth Whittaker designed the elements of the ISARIC Paediatric COVID-19 follow-up questionnaire which were incorporated into the online questionnaire used in this study to which all the CLoCk Consortium members contributed.

All members of the CLoCk Consortium made substantial contributions to the conception or design of the work; were involved in drafting both the funding application and this manuscript; approved the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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10

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13
14

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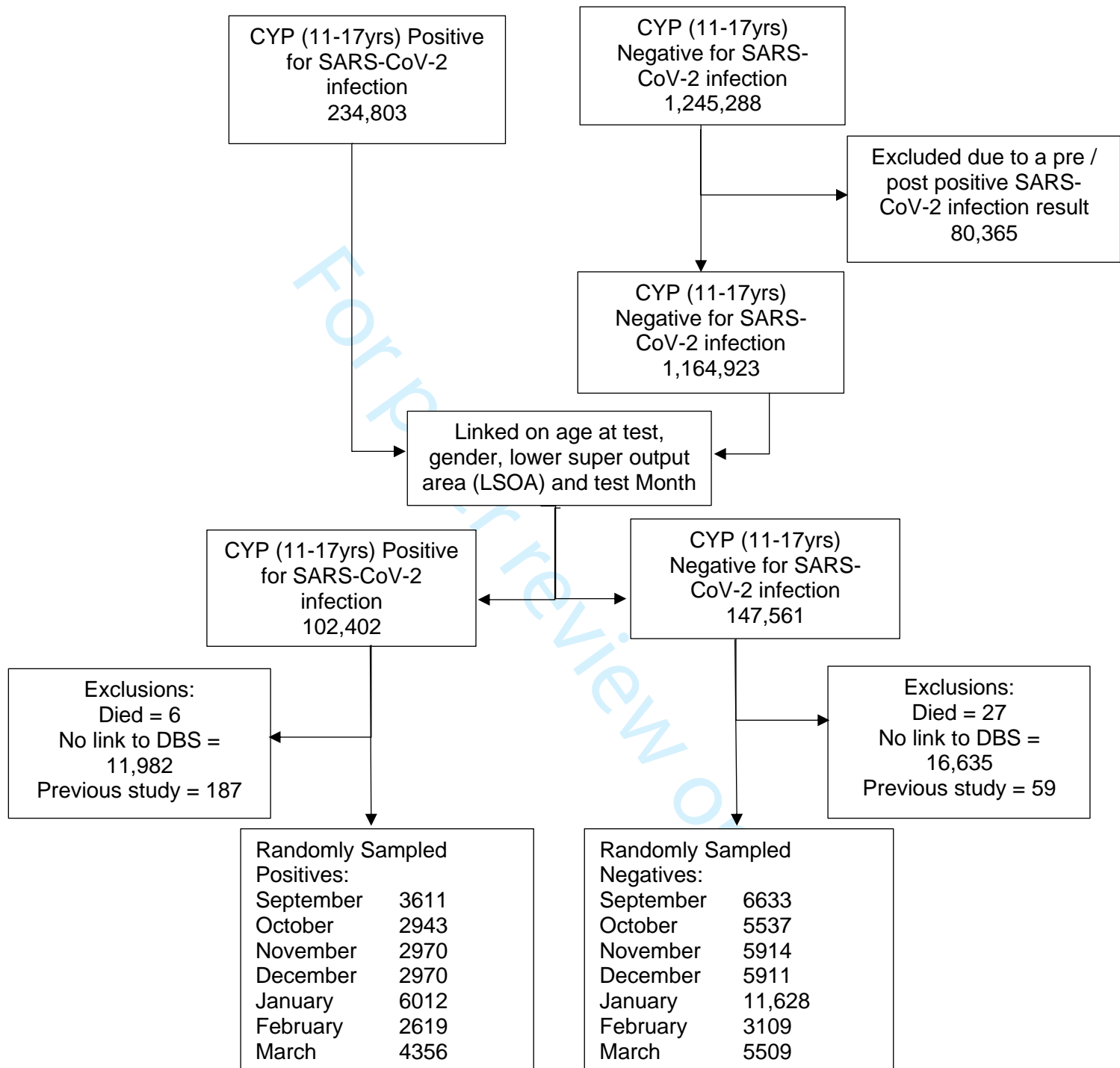
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3 **Figure 1:** Flowchart of the selection process.
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Figure 1: Flowchart of the selection process.



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Long Covid and the mental and physical health of children and young people: national matched cohort (CLOCK) study protocol

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4 matched cohort (CLoCk) study protocol
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Abstract

Introduction: There is uncertainty surrounding the diagnosis, prevalence, phenotype, duration and treatment of Long COVID. This study aims to (a) describe the clinical phenotype of post-COVID symptomatology in children and young people (CYP) with laboratory-confirmed SARS-CoV-2 infection compared to test-negative controls, (b) produce an operational definition of Long COVID in CYP, and (c) establish its prevalence in CYP.

Methods and analysis: A cohort study of SARS-CoV-2 positive CYP aged 11-17 years compared with age-, sex- and geographically-matched SARS-CoV-2 test-negative CYP. CYP aged 11-17 testing positive and negative for SARS-CoV-2 infection will be identified and contacted 3, 6, 12 and 24 months after the test date. Consenting CYP will complete an online questionnaire. We initially planned to recruit 3,000 test positives and 3,000 test negatives but have since extended our target. Data visualisation techniques will be used to examine trajectories over time for symptoms and variables measured repeatedly, separately by original test status. Summary measures of fatigue and mental health dimensions will be generated using dimension reduction methods such as latent variables/latent class/PCA methods. Cross-tabulation of collected and derived variables against test status and discriminant analysis will help operationalise preliminary definitions of Long COVID.

Ethics and Dissemination: Research Ethics Committee Approval granted. Data will be stored in secure Public Health England (PHE) servers or University College London's Data Safe Haven. Risks of harm will be minimised by providing information on where to seek support. Results will be published on a pre-print server followed by journal publication, with reuse of articles under a CC BY licence. Data will be published with protection against identification when small frequencies.

Study registration: Study registered with ISRCTN: Trial ID: ISRCTN34804192 and granted Urgent Public Health prioritisation.

Article Summary

STRENGTHS

- This study does not start with an arbitrary definition of a new condition – ‘opinion-based medicine’
- Rather it represents ‘evidence-based medicine’ - we will seek the views of children and young people on what they have experienced physically and mentally in the months following COVID-19
- The study incorporates a comparator matched cohort of children and young people who have experienced a pandemic, school closure and social isolation but who had a negative COVID test

WEAKNESSES

- The comparator matched cohort of children and young people must also have had a reason to seek a COVID test: symptoms, anxiety, a contact or a bereavement
- Ideally, we would test all children for antibodies to confirm COVID-19 positive and negative status throughout the study period but we thought would significantly reduce participation

Introduction

Currently, there is huge uncertainty surrounding the diagnosis, prevalence, phenotype, duration and treatment of Long COVID. There is currently no diagnostic test or code for Long COVID. Consequently, cases of Long COVID are not captured in routine National Health Service (NHS) administrative datasets. Instead, Long COVID may be coded as a variety of different conditions in hospital or symptom clusters in non-hospitalised children and young people (CYP). However, it is possible the symptoms associated with Long COVID are in fact a mixture of factors relating to the pandemic and lockdown as a whole rather than the viral infection itself. For example, factors such as social isolation, anxiety, depression or educational concerns may be the root cause of these symptoms in CYP both with and without SARS-CoV-2 infection. The effects on the developing brain and behaviour of adolescents could be far reaching¹.

Despite acute COVID-19 illness being milder in CYP, it should not be assumed that those CYP at low risk of life-threatening acute infections^{2,3} do not suffer the longer-term consequences of SARS-CoV-2 infection. It is important to study Long COVID within this population given that the psychological and social impact of Long COVID could have major consequences for transition to adulthood. There is a clear need to define the clinical phenotype of Long COVID in order to understand those most at risk, the illness trajectory and to provide accurate information on the natural course of the condition. It is equally important to understand both the physical and mental health impact on CYP with Long COVID, given the rise in mental health problems among CYP since the start of the pandemic⁴. Obtaining a better understanding of which CYP are affected will help with targeting potential interventions.

The greatest risk factor for severe acute SAR-CoV-2 illness has been old age, with other risk factors at all ages including obesity, comorbid long-term conditions, learning and neurological disabilities, mental health problems and ethnic minority status. It is plausible that such CYP may be most at risk of suffering from Long COVID, given that much is still unknown in CYP about the immunological susceptibility and underlying biology of Long COVID. Of all CYP, those likely to be most at risk of Long COVID are teenagers, with existing literature showing they make up the majority of CYP with chronic fatigue, post viral syndromes and persistent symptoms⁵.

In adults, there is emerging evidence that gender is a risk factor for Long COVID, with middle-aged females more susceptible than men⁶. In terms of symptoms, two main groupings have been identified (i) respiratory symptoms (e.g., cough, shortness of breath) as well as fatigue and headaches, and (ii) multi-system, including the brain, gut and heart. Among adults with Long COVID, heart symptoms such as palpitations or fast heartbeat, pins and needles or numbness and problems concentrating ('brain fog') have been reported. Experiencing a greater number of symptoms during the first week of infection, as well as older age, have also been linked to Long COVID. It should be noted mental health conditions were not reported in this cohort. Four syndromes have been described in adults: Post-viral fatigue; Fluctuating multi-system symptoms; Post-intensive care syndrome; and Lasting organ damage. It is known in both adults and young people that a wide range of long-term physical conditions increase the risk of mental ill-health, particularly if the condition involves the central nervous system, with several studies

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3 reporting increased rates of all common mental health conditions in children⁷. Moreover, fatigue
4 has also been studied in paediatric long-term conditions including CYP with multiple sclerosis^{8 9}.
5 Emerging clinical observations and preliminary research indicate that COVID-19 can have a
6 long-term impact on CYP in a range of domains^{10 11} but well conducted, methodologically robust
7 studies are lacking.
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10 This study primarily aims to (a) describe the clinical phenotype and prevalence of post-COVID
11 symptoms (e.g., pain or physical symptoms, fatigue, sleep problems, mental health problems)
12 among test positive and test negative CYP, (b) produce an operational definition of Long COVID
13 in CYP, and (c) establish the prevalence of Long COVID in CYP testing positive for SARS-CoV-
14 2 infection. The second aim is of particular importance given that this is a prerequisite for any
15 future epidemiological or interventional study. This will be achieved by using the empirical data
16 we will acquire from 17,000 CYP and a national Delphi consensus process.
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20 **Methods**

21 *Study design and setting*

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25 Public Health England (PHE) has been conducting national surveillance of SARS-CoV-2 since
26 the start of the pandemic in England. PHE receives daily electronic notifications of all SARS-
27 CoV-2 RT-PCR tests performed in healthcare settings (Pillar 1 tests) and in the community
28 (Pillar 2 tests), which are reported through the Second Generation Surveillance System (SGSS).
29 Information within the SGSS reports includes NHS number, name, age, sex, postcode, date of
30 sample, reporting laboratory and test result. PHE also has access to the electronic Patient
31 Demographic Service (PDS), which contains the names, addresses and status (alive/dead) of
32 all patients registered with the NHS.
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36 A sample of CYP aged 11-17 years old when testing positive for SARS-CoV-2 between
37 September 2020 and March 2021 and COVID test-negative CYP matched for age, sex and
38 region identified through SGSS will be linked to PDS using available identifiers and postal
39 addresses. A letter will be posted to them, informing them about the study and inviting them to
40 take part using an online link. This link will provide them with information about the study, with
41 an option to consent online and complete a short recruitment questionnaire (or both as paper
42 options). Recruitment was planned to start in March 2021 and all data collection anticipated to
43 end in April 2023.
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47 This will be a cohort study of SARS-CoV-2 test-positive CYP aged 11-17 years matched on the
48 test date, age, sex and geography to SARS-CoV-2 test-negative controls identified by PHE.
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50 *Participants*

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53 Between September 2020 and March 2021, 234,803 CYP aged between 11 and 17 years were
54 diagnosed with COVID-19 in England. During the same period there were 1,481,154 negatives
55 tests among this age group equivalent to 1,203,996 CYP. Among those who tested negative
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3 76,689 individuals (100,154 tests) were excluded as they had a positive result pre and/or post
4 their negative test. The positive and negative cohorts were linked using age at test, gender, month
5 of test, and lower super output area resulting in 102,402 positive individuals and 147,561 negative
6 individuals. Matched individuals were checked against the NHS spine to exclude any individuals
7 who have died, and to extract participants addresses to send invitation letters. 37 individuals were
8 excluded because they had died since their COVID-19 test (6 among those positive and 31 among
9 those negative), and 11,193 individuals of the positive cohort and 19,251 individuals of the
10 negative cohort were excluded as an address was not available. Finally, 246 CYP were excluded
11 as they were included in a previous study. Following exclusions 91,016 positive CYP and 128,220
12 negative CYP will be available to be invited to participate in the study. For all the months except
13 December, all eligible individuals will be sent an invitation. For those tested in December, 2,970
14 positive CYP and 5,911 negative CYP will be invited as the eligible number was so large that
15 additional funding would be needed to invite all those eligible.
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20 This is shown schematically in Figure 1.
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22 *Data collection*

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25 Participating families of CYP will be contacted 3, 6, 12 and 24 months after the CYP's SARS-
26 CoV-2 test (depending on recruitment month) and invited to take part in the study. Following
27 online informed consent, the CYP will self-complete an online (or paper) questionnaire about
28 their mental and physical health. CYP towards the lower end of the 11-17 age band and CYP
29 with special educational needs or disability may require the help of a carer to complete the
30 questionnaire.
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33 *Outcomes*

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36 The questionnaires given to CYP include elements of the ISARIC Paediatric COVID-19 follow-
37 up questionnaire¹² and the recent Mental Health of Children and Young people in England
38 surveys¹³ to facilitate international comparisons regarding the risk factors and profile of Long
39 COVID in CYP. The questionnaires given to CYP were designed together with the International
40 Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Paediatric Working
41 Group to produce a harmonised data collection tool, allowing for standardisation and
42 metanalysis by design.
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46 The elements taken from the ISARIC Paediatric COVID-19 follow-up questionnaire¹² include
47 questions about demographics and physical symptoms, with particular questions enquiring
48 about cough and fever, given that these are the main acute symptoms in non-hospitalised
49 CYP¹⁴ and gastrointestinal symptoms, as a study has shown such symptoms were common in
50 seropositive CYP¹⁵. It is likely other symptoms will manifest later in Long COVID (e.g., tiredness,
51 headaches, myalgia etc.), with the skin rashes and cardiac problems in hospitalised children
52 with paediatric multisystem inflammatory syndrome being borne in mind for Long COVID⁵.
53 Those older CYP could very well overlap with adult symptomatology (e.g., a neuropsychiatric-
54 encephalitic sub-group).
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4 In terms of the other questions, the Strengths and Difficulties Questionnaire (SDQ)¹⁶ will be
5 used to assess emotional and mental health, consisting of 25 items. The EQ-5D-Y¹⁷ will be used
6 as a measure of quality of life/functioning, with fatigue measured using the 11-item Chalder
7 Fatigue Questionnaire (CFQ)¹⁸. Additionally, the short, 7-item version of The Warwick
8 Edinburgh Mental Wellbeing Scale (WEMWBS)¹⁹ will be included. Loneliness will be measured
9 using the 4-item UCLA Loneliness Scale for Children²⁰ as well as self-reported school
10 attendance.
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14 The length of the online self-assessment has an estimated completion time of approximately 20
15 minutes for CYP. The CYP do not have to complete all of the questions at once but can pause
16 and save the answers at any point.
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18 *Statistical analyses*

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21 Response rates for positive and negative CYP will inform expectations of final study size and
22 possibly refinement of the sampling percentages. Descriptive statistics will be used for all
23 dimensions collected at baseline and the follow-up questionnaires, separately by test status,
24 wave and month of test. Appropriate data visualisation techniques will be used to examine
25 trajectories over time for those variables that are measured repeatedly, separately by test status
26 and month of test. Summary measures of the fatigue and mental health dimensions will be
27 generated using dimension reduction methods such as latent variables/latent class/PCA
28 methods. Cross-tabulation of latent variables against test status as well as discriminant analysis
29 will help operationalise preliminary definitions of Long COVID. These will be compared with
30 definitions based on categorisation of prolonged symptoms supplemented by a Delphi
31 consensus process.
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35 *Sample size*

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38 A total of 5,000 participants (2,500 test-positive and 2,500 test-negative) would give 80% power
39 to detect at least a 4% difference in symptoms at 5% significance, if the COVID-19 negative
40 participants had a prevalence similar to that reported for adults (i.e., 34%). Greater baseline
41 prevalences (e.g., 40%) would require slightly greater numbers for the same power and
42 confidence; smaller baseline prevalences (e.g., 20%) smaller numbers. However, identifying risk
43 factors for long COVID-19 would require studying demographic, social, family and clinical data
44 and thus we would require larger numbers. For this reason, we are planning to invite all
45 available participants.
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49 *Patient and Public Involvement*

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51 Resources have been allocated for any Patient and Public Involvement (PPI) activities at
52 INVOLVE rates including a nationally representative PPI research advisory group. PPI members
53 will be offered training and support in accordance with the INVOLVE²¹ report and other
54 guidance²² including online training. PPI meetings will take place quarterly.
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Ethics and Dissemination

Ethical considerations

PHE has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for national surveillance of communicable diseases. Individual patient consent is not required for initial invitation to the study. Parents/carers and young people will be sent an invitation with a link to the website with the relevant information sheets and consent forms. They will have the opportunity to ask any questions about the study. Parents/carers of CYP under 16 years of age will be asked to complete a Parent/carer consent form. The young person will also be asked to sign an assent form to indicate their agreement. 16-17-year-olds will be asked for consent (using the Young Person Consent Form); but their parents will not. This is in line with Health Research Authority recommended processes²³.

Study approved by Yorkshire & The Humber - South Yorkshire Research Ethics Committee (REC reference: 21/YH/0060; IRAS project ID:293495).

It is possible that the questionnaires may make some vulnerable participants feel fatigued or distressed from completing questionnaires relating to their mental health and/or report serious symptoms that put them at immediate risk. The research team will provide information on where to seek support and provide self-help information. Unfortunately, the researchers are unable to provide medical advice. However, existing national surveys of children's mental health also follow this risk protocol.

Dissemination

Peer reviewed publications, briefings for policy makers and lay summaries for participants and CYP and carers. Results will be made public, initially on a pre-print server and we will allow reuse of articles under a CC BY licence. The dataset will be made publicly available.

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3 **Figure 1:** Flowchart of the selection process.
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Terence Stephenson t.stephenson@ucl.ac.uk conceived the idea for the study, submitted the successful grant application and undertook the first revision of the manuscript.

Roz Shafran r.shafran@ucl.ac.uk provided ideas on mental health follow up to the original grant application, submitted the ethics and R&D applications and revised the manuscript.

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Maria Zavala Maria.Zavala@phe.gov.uk undertook a separate pilot study which informed the CLoCk consent process and the online questionnaire.

Ruth Simmons Ruth.Simmons@phe.gov.uk designed the participant sampling and dataflow.

Shamez Ladhani shamez.ladhani@phe.gov.uk operationalised the regulatory and recruitment ideas for the study and revised the manuscript.

Olivia Swann and Elizabeth Whittaker designed the elements of the ISARIC Paediatric COVID-19 follow-up questionnaire which were incorporated into the online questionnaire used in this study to which all the CLoCk Consortium members contributed.

All members of the CLoCk Consortium made substantial contributions to the conception or design of the work; were involved in drafting both the funding application and this manuscript; approved the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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13
14

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21 Department of Health
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25 **Data Sharing:** Applications for relevant anonymised data should be submitted to the PHE office
26 for Data Release: [https://www.gov.uk/government/publications/accessing-public-health-england-](https://www.gov.uk/government/publications/accessing-public-health-england-data/about-the-phe-odr-and-accessing-data)
27 [data/about-the-phe-odr-and-accessing-data](https://www.gov.uk/government/publications/accessing-public-health-england-data/about-the-phe-odr-and-accessing-data)
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Figure 1: Flowchart of the selection process.

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