Public Health England

GREAT ORMOND STREET INSTITUTE OF CHILD HEALTH

Children and young people with Long Covid

CLoCK

Principal investigator: Professor Roz Shafran
Funding: NIHR
Grant reference: COV-LT-0022
Duration of project: 1June 2020 to 1 September 2021

Amendment history

The following amendments and/or administrative changes have been made to do this protocol since the implementation of the first approved version.

Amendment number	Protocol version umber	Date	Summary of changes

Contents

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Study summary

Study title:
Tracking the impact of Covid-19 on the mental health of children, young people and families; follow up of a national longitudinal probability sample.

Study short title:
Children & young people with Long Covid (CLoCk) study.

Research question and/or aim(s):

- to describe the clinical phenotype and prevalence of post-COVID symptomatology (for example, fatigue, breathlessness, post exertional myalgia, sleep problems, muscle or joint pain, headaches, tics, sore throat, mental health problems including low mood, anxiety, self-harm, eating problems, problems thinking, remembering or concentrating (brain fog), flu-like symptoms, feeling dizzy or sick, palpitations) symptoms in test +ve and test -ve CYP
- to use these data to produce an operational definition of long COVID in CYP, a pre-requisite for any future epidemiological or interventional study – for example, an RCT of a graded activity intervention or rehabilitative approach as has been used for CFS (NICE guidance under review); "Pandemic policy must include defining and measuring what we mean" (1), which can be done either by:
    - using the Dutch model of a national consensus methodology to define a chronic condition in children which can be used for epidemiological and interventional research (a national Delphi consensus process)
    - or using a centile of a basket of prolonged symptoms with a continuous quantity/score; that is, if some CYP who have tested positive for COVID experience a mixture of various symptoms for variable periods, we confine a diagnostic definition of long COVID to the 10% (say) at the most extreme end of this spectrum
- to establish the prevalence of long COVID in CYP who have tested positive for SARS-CoV-2 and progress to a more detailed definition of the profile including more intensive study of a sub-group, for example non-invasive biological tests, psychological tests of cognitive functions, detailed psychiatric assessment, and qualitative interviews of experience to search for additional symptoms. These data will be needed to inform future NHS services and policy.

Study design:
Longitudinal cohort of SARS-CoV-2 positive CYP aged 11 to 17 years 364 days on the test date (hereafter 11 to 17) compared with age, sex and region matched SARS-CoV-2 test negative controls ('cohort-analytic' study), identified by PHE.

Study participants:
Young people 11 to 17 years old when tested for SARS-CoV-2 during 3 individual months separated by 3-month intervals (Sept 2020, Dec 2020, Mar 2021).

Introduction

Background and rationale

1. What is the problem to be addressed?
Uncertainties relate to diagnosis, prevalence, phenotype, duration and treatment of long COVID. Whilst we can show children and young people (CYP) have antigen or antibody for SARS-CoV-2 there is no diagnostic test or code for long COVID, which is therefore not captured in routine NHS administrative datasets. Long COVID may be coded as a number of different conditions or symptom clusters in non-hospitalised CYP. It is possible that the symptoms described may be due to a mixture of factors related to the COVID pandemic and 'lockdown' rather than viral infection per se, including social isolation, anxiety and depression or educational concerns – with or without evidence of SARS-CoV-2 infection. The effects on the developing brain and behaviour of the adolescent could be far reaching (15).

2. Why is this research important in terms of improving the health and/or wellbeing of the public and/or to patients and health care services?
Ongoing symptoms following SARS-CoV-2 infection have been described anecdotally in all age groups. There is a real risk, as in the early stages of the COVID-19 pandemic, that CYP are missed out from research and follow-up, which is confined by default to consenting adults over 18 years. Whilst acute COVID-19 illness has been milder in CYP, we should not assume that CYP who are at low risk of life-threatening acute infections (19), (22) do not suffer the longer-term consequences that older people seem to. The psychological and social impacts of long COVID, and the effects of the pandemic, if sustained over a prolonged period, could have major consequences for the transition to adulthood, particularly if CYP receive little support for symptoms with the potential to derail development and function. There is a need to define the clinical phenotype to help understand which subgroups are most at risk, the illness trajectory and to provide accurate information for CYP and their carers about the progression and the natural course of the condition. Understanding the mental health and wellbeing trajectory alongside physical symptoms is crucial, particularly given the rise in mental health problems in CYP since the start of the pandemic (16). Better understanding of which CYP are affected will help with targeting potential interventions and remediations.

3. Review of existing evidence – how does the existing literature support this proposal?
Little is known about the characteristics, risk factors, progression or outcomes of long COVID, even in adults. The greatest risk factor for severe acute SARS-CoV-2 illness has been old age. Other risk factors at all ages include obesity, co-morbid long-term conditions, learning and neurological disabilities, mental health problems and ethnic minority status; all groups under-represented in CYP research generally. It is plausible that

these could also be the CYP most at risk from long COVID, given that so much is still unknown in CYP about the immunological susceptibility and underlying biology of long COVID, so it would be essential to explore these high-risk subgroups. The population of CYP likely to be most at risk of long COVID are teenagers as existing evidence shows they are the vast majority of CYP with chronic fatigue, post viral syndromes and persistent symptoms. Ludvigsson (2020) (10) reported COVID positive CYP with median age 12 yrs with symptoms longer than 6 months. Depression, anxiety and fatigue may occur in teenagers post-viral illness, including influenza, influencing the developing brain. In adults, there is emerging evidence (18) that gender is a risk factor for long COVID (females > males, especially in the younger age group). Two main symptom groupings were identified, one dominated by respiratory symptoms such as cough and shortness of breath, as well as fatigue and headaches, and the second form was multi-system, including the brain, gut and heart. Adults with long COVID also reported heart symptoms such as palpitations or fast heartbeat, as well as pins and needles or numbness, and problems concentrating ('brain fog'). Greater number of symptoms in the first week of infection, as well as older age, were also associated with long-COVID. Mental health conditions were not reported in this cohort. 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, and several studies have reported increased rates of all common mental health conditions in children (11). Fatigue has also been studied in paediatric long-term conditions including CYP variants of multiple sclerosis (2), (3).

Aims and Objectives

The aims of this study are:

- to describe the clinical phenotype and prevalence of post-COVID symptomatology (for example, fatigue, breathlessness, post exertional myalgia, sleep problems, muscle or joint pain, headaches, tics, sore throat, mental health problems including low mood, anxiety, self-harm, eating problems, problems thinking, remembering or concentrating (brain fog), flu-like symptoms, feeling dizzy or sick, palpitations) symptoms in test +ve and test -ve CYP
- to use these data to produce an operational definition of long COVID in CYP, a pre-requisite for any future epidemiological or interventional study – for example, an RCT of a graded activity intervention or rehabilitative approach as has been used for CFS (NICE guidance, under review); "Pandemic policy must include defining and measuring what we mean" (1), which can be done either by:
    - using the Dutch model of a national consensus methodology to define a chronic condition in children which can be used for epidemiological and interventional research (a national Delphi consensus process)

    - or using a centile of a basket of prolonged symptoms with a continuous quantity/score; that is, if some CYP who have tested positive for COVID experience a mixture of various symptoms for variable periods, we confine a diagnostic definition of long COVID to the 10% (say) at the most extreme end of this spectrum
- to establish the prevalence of long COVID in CYP who have tested positive for SARS-CoV-2

Methods

Setting and/or population

PHE has been conducting national surveillance of SARS-CoV-2 since the start of the pandemic in England. PHE receive daily electronic notifications of all SARS-CoV-2 RT-PCR tests performed in healthcare settings (Pillar 1 tests) and in the community (Pillar 2 tests) and the results of their test through the Second Generation Surveillance System (SGSS). Information within the SGSS reports includes NHS number, name, age, sex, postcode, date of sample, reporting laboratory and test result. PHE also has access to the electronic Patient Demographic Service (PDS), which contains the names, addresses and status (alive/dead) of all patients registered with the NHS.

For this study 15,000 CYP 11 to 17 years old when tested positive for SARS-CoV-2 during 3 individual months separated by 3-month intervals (Sept 2020, Dec 2020, Mar 2021) and the same number matched for age, sex and region identified through SGSS will be linked to PDS using available identifiers and their postal addresses received. These will then be used to write a letter that will be posted to them, informing them about the study and inviting them to take part using an online link. This link will provide them with information about the study, an option to consent online and complete a short recruitment questionnaire

Design

A longitudinal cohort of SARS-CoV-2 positives aged 11 to 17 years compared with age, sex and region matched SARS-CoV-2 test negative controls (‘cohort-analytic’ study), identified by PHE.

Sample

Eligible participants will be those that have had a Covid-19 test between 1 September 2020 and 28 February 2021. Participants will be recruited in a ratio of 1:1:2 with twice as

many participants being recruited in months January and February compared to September to October, and November to December in order to reduce recall bias.

Using the PHE COVID tests conducted between the months of September 2020 and March 2021, we plan to construct 2 groups of 10,000 CYP (5,000 positive tests and 5,000 negative). This sample, potentially captured within specified monthly time frames of 5,000 “exposed” and 5,000 “unexposed”, will be contacted, anticipating recruiting 20% in each group, as estimated by CYP recruitment rates in other PHE studies on COVID-19 (8). We do not anticipate that CYP (except perhaps small numbers at high risk) will have received mass COVID vaccination by March 2021 although of course test positive rates may fall as a result of social distancing and the initial vaccination of healthcare workers and older and high-risk adults.

Families of CYP within these cohorts will be contacted 6, 12 and 24 months after the CYP’s SARS-CoV-2 test (depending on recruitment month) and invited to take part in the study. With online informed consent, the CYP will self-complete an online questionnaire about their mental and physical health (see below). CYP towards the lower end of the 11 to 18 age band and CYP with SEN or disability may require the help of a carer.

Data collection

Following very careful consideration, and given that the length of the online self-assessment must not be prohibitive, the mental and physical health self-report measures to be included are below. The measures include elements of the ISARIC Paediatric COVID-19 follow-up questionnaire (17) and the recent Mental Health of Children and Young people in England surveys (13) to facilitate international comparisons regarding the risk factors and profile of Long COVID in CYP. Self-completion will take approximately 20 minutes. We also plan to ask for consent to contact participants at a later date about further studies where more in-depth measures could be used.

For the purposes of this proposal though, we consider the following to be central:

- ISARIC Paediatric COVID-19 follow-up subset of questions including:
    - demographic
    - physical symptoms – cough and fever are the main acute symptoms in non-hospitalised CYP (9). A UK study has shown that gastrointestinal symptoms were common in CYP who were seropositive (21). It is likely other symptoms will manifest later in long COVID (typically tiredness, headaches, myalgia, arthralgia, IBS-like symptoms in CYP with post-viral syndromes) and the skin rashes and cardiac problems in hospitalised children with Paediatric multisystem inflammatory syndrome should be borne in mind for long COVID

(10). Older CYP could overlap with adult symptomatology for example, a neuropsychiatric-encephalitic sub-group
    - Strengths and Difficulties Questionnaire to assess emotional and mental health (25 items; (5))
    - quality of life/functioning – EQ-5D-Y (23)
- Chalder Fatigue Questionnaire – CFQ (4) – 11 items.
- short version of The Warwick Edinburgh Mental Wellbeing Scale – WEMWBS (20) – 7 items
- Loneliness – Adapted UCLA 4 items (14); Self-reported school attendance as a percentage. We hope to conduct a separate, complementary study that will link our findings with the National Pupil Database.

Data Storage

All data will be stored electronically and there will not be any physical storage.

Electronic data will be collected and stored in secure PHE servers. Study investigators requiring access to personal identifiable information (to contact participants for missing information or complete additional questionnaires) will be PHE employees or PHE honorary contract holders. Data will be routinely cleaned and pseudonymised (to allow longitudinal tracking) for analysis within the team. In the event that any personal data (such as email addresses) are required to be stored elsewhere, such data will be kept within the secure UCL (Data Safe Haven) system.

Professor Bianca De Stavola will have control of and act as the custodian for the data generated by the study.

Personal data will be stored or accessed for 6 to12 months after the study has ended and research data generated by the study will be stored for 20 years.

Research data will be stored in UCL's Data Safe Haven. It will only be accessed by members of the research team. The Data Safe Haven has been certified to the ISO27001 information security standard and conforms to NHS Digital's Information Governance Toolkit. Built using a walled garden approach, where the data is stored, processed and managed within the security of the system, avoiding the complexity of assured end point encryption.

Data analysis

We will be using mixed model simulations and data from the first cohort to estimate the power and refine the sample size as part of the funded bid which includes a Professor of Statistics as a co-applicant who has been involved from the beginning in constructing this research plan.

Study Management

Project timescales and key milestones

The key milestones and stages in the project are as follows:

Phase	Activity	Date(s)
Set up	UCL Unitemp post-doc search starts	January 2021
	Substantive GOSH admin and UCL post-doc advert placed	January 2021
	Substantive GOSH admin and UCL post-doc: convene panel, short-listing and virtual interviews, references, pre-employment checks	January 2021
	PHE Project Manager advert placed	January 2021
	PHE Project Manager: convene panel, short-listing and virtual interviews, references, pre-employment checks	February 2021
	Ethical permission applied for	January 2021 – February 2021
	Ethical permission received	February 2021
	R&D approval applied for	February 2021
	R&D approval received	March 2021
	PHE Project Manager, Post-doc and GOSH Admin Starts	February 2021 – January 2024
	Post-doc gains permissions to use PHE systems until PHE Project Manager in post	February 2021
	Recruitment for PPI group to ensure broad and diverse representation	February 2021 – May 2021
	Statistical modelling to estimate and refine sample size	January 2021 – January 2022
September 2020 cohort	Post-doc uses PHE systems to find addresses of 10,000 CYP tested in Sept 2020 and contacts them for 6-month follow up	March 2021 – April 2021

	22% of 10,000 CYP tested in Sept 2020 respond, some requiring up to 3 postal reminders	March 2021 – April 2021
	Analysis of 6-month FU for Sept 2020 cohort	May 2021 – June 2021
	Output/Progress Report - Long COVID in CYP at 6-month post COVID-Test based on Sept 2020 cohort	July 2021 – August 2021
	Post-doc sends out 12-month follow-up measures for Sept 2020 Cohort	September 2021 – October 2021
	12-month responses received	September 2021 – October 2021
	Analysis of 12-month FU for Sept 2020 Cohort	November 2021 – December 2021
	Output/Progress Report - Long COVID in CYP at 12-month post COVID Test based on Sept 2020 cohort	January 2022 – February 2022
	Post-doc sends out 24-month follow-up measures for Sept 2020 cohort	September 2022 – October 2022
	24-month responses received	September 2022 – October 2022
	Analysis of 24-month FU for Sept 2020 Cohort	November 2022 – December 2022
	Output/Progress Report and Dissemination Activities - Long COVID in CYP at 24-month post COVID Test based on Sept 2020 cohort	January 2023 – February 2023
December 2020 cohort	PHE Project Manager uses PHE systems to find addresses of 10,000 CYP tested in Dec 2020 and contacts them for 3-month follow up	March 2021 – April 2021
	22% of 10,000 CYP tested in Dec 2020 respond, some requiring up to 3 postal reminders	March 2021 – April 2021

	Analysis of 3-month FU for Dec 2020 cohort	May 2021 – June 2021
	Output/Progress Report - Long COVID in CYP at 3-month post COVID Test based on Dec 2020 cohort	July 2021 – August 2021
	Post-doc sends out 6-month follow-up measures for Dec 2020 cohort	June 2021 – July 2021
	6-month responses received	June 2021 – July 2021
	Analysis of 6-month FU for Dec 2020 Cohort	August 2021 – September 2021
	Output/Progress Report - Long COVID in CYP at 6-month post COVID Test based on Sept 2020 and Dec 2020 cohort	October 2021 – November 2021
	Post-doc sends out 12-month follow-up measures for Dec 2020 cohort	December 2021 – January 2022
	12-month responses received	December 2021 – January 2022
	Analysis of 12-month FU for Sept and Dec 2020 Cohort	February 2022 – March 2022
	Output/Progress Report - Long COVID in CYP at 12-month post COVID Test based on Sept and Dec 2020 cohort	April 2022 – May 2022
	Post-doc sends out 24-month follow-up measures for Dec 2020 cohort	December 2022 – January 2023
	24-month responses received	December 2022 – January 2023
	Analysis of 24-month FU for Sept and Dec 2020 Cohort	February 2023 – March 2023
	Output/Progress Report and Dissemination Activities- Long COVID in CYP at 24-month post COVID Test based on Sept and Dec 2020 cohort	April 2023 – May 2023
Inception cohort	PHE Project Manager uses PHE systems to find addresses of 10,000 CYP tested in March 2021 and contacts them for 1-month follow up	April 2021 – May 2021

	22% of 10,000 CYP tested in March 2021 respond, some requiring up to 3 postal reminders	April 2021 – May 2021
	Post-doc sends out 3-month follow-up measures for March 2021 cohort	June 2021 – July 2021
	3-month responses received	June 2021 – July 2021
	Analysis of 1 and 3-month FU for March 2021 and 3-month FU for Dec 2020 Cohort	August 2021 – September 2021
	Output/Progress Report - Long COVID in CYP at 1 and 3-month post COVID Test based on March 2021 and Dec 2020 cohort	October 2021 – November 2021
	Post-doc sends out 6-month follow-up measures for March 2021 cohort	September 2021 – October 2021
	6-month responses received	September 2021 – October 2021
	Analysis of 6-month FU for all cohorts	November 2021 – December 2021
	Output/Progress Report - Long COVID in CYP at 6-month post COVID Test based on all cohorts	January 2022 – February 2022
	Post-doc sends out 12-month follow-up measures for March 2021 cohort	March 2022 – April 2022
	12-month responses received	March 2022 – April 2022
	Analysis of 12-month FU for all cohorts	May 2022 – July 2022
	Output/Progress Report - Long COVID in CYP at 12-month post COVID Test based on all cohorts	August 2022 – October 2022
	Post-doc sends out 24-month follow-up measures for March 2021 cohort	March 2023 – April 2023
	24-month responses received	March 2023 – April 2023
	Analysis of 24-month FU for all cohorts	May 2023 – July 2023

	Output/Progress Report and Dissemination Activities - Long COVID in CYP at 24-month post COVID Test based on all cohorts	August 2023 – October 2023
Meetings	PPI Meetings	February 2021
		May 2021
		August 2021
		November 2021
		February 2022
		May 2022
		August 2022
		November 2022
		February 2023
		May 2023
		August 2023
		November 2023
	Monthly Co-applicant Meetings	January 2021 – January 2024
	Weekly then fortnightly management meetings between UCL, GOSH and PHE	January 2021 – January 2024
General	Writing to all participants with findings	November 2023 – December 2023
	Stakeholder and public meeting to disseminate findings	November 2023 – December 2023
	International comparisons of phenotype, prevalence, and progression via ISARIC	August 2023 – October 2023
	Closing study	December 2023 – January 2024

Stephenson and Shafran will meet weekly initially with the 3 dedicated staff to ensure the project stays on track with the projected timelines in the attached Gantt chart. Once the first cohort has been identified and the postal invites sent out, the frequency of

meetings can be reduced to fortnightly. Stephenson, Ladhani, Shafran and Heyman will meet monthly as a minimum with co-applicants from across the UK. The new ways of virtual working which the COVID pandemic has prompted allow this frequency of meetings without the need for travel or senior staff taking large amounts of time out to attend in person.

Patient and participant involvement
As engagement of CYP and their carers is crucial to the investigation of long COVID in school-aged children, we have a PPI co-applicant who will lead this work. We have allocated resources for this role and any PPI activities at INVOLVE rates.

PPI members will be offered training and support in accordance with the INVOLVE (7) report and other guidance (12). When recruiting members to the PPI group, training and support needs will be discussed and a bespoke programme will be developed, including online training.

Data management and information governance
We will manage all information related to participants in accordance with the General Data Protection Regulation, Data Protection Act, NHS Caldicott Principles, the Research Governance Framework for Health and Social Care, and all conditions of the Research Ethics Committee Approval. All researchers will have received GDPR training. Only named members of the study team will have access to the data stored in PHE and UCL secure data environments. All data is regularly backed up on the University's secure servers.

Ethics

Consent

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 andcarers 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.

1. Parents and/or carers of CYP<16 will be asked to complete a Parent and/or carer consent form. The young person will also be asked to sign an assent form to indicate their agreement.

2. 16 to 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 processes (6).

If the participant wishes to take part, electronic consent will be obtained in accordance with HRA guidelines.

Harms

It is possible that the questionnaires may make some vulnerable participants feel fatigued.

Participants may also feel 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 and responses are not analysed immediately. However, existing national surveys of children's mental health also follow this risk protocol.

We will minimise risks of harm by:

- the questionnaire explicitly states it does not need to be completed in one go which is hoped to mitigate fatigue
- providing information on where to seek support and provide self-help information

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Published March 2021
PHE gateway number: GOV-7858

PHE supports the UN Sustainable Development Goals

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