

Short Report on Long COVID

22.7.2021

This report is provided at the request of SAGE and includes information from ongoing studies investigating long COVID including the COVID-19 Longitudinal Health and Wellbeing National Core Study-CONVALESCENCE Study, REACT-2, PHOSP-COVID, ONS's COVID-19 Infection Survey (CIS) and the COVID Symptom Study App.

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This report provides evidence to a selection of priority questions on long COVID. For the full list of questions, please refer to the appendix.

Part 1: Questions we can (partially) answer now

Part 2: Questions we may be able to answer later

1. Questions we can (partially) answer now

Q1 DEFINITION - How can we define Long COVID, disaggregating the various syndromes from each other? What are the clinical diagnostic criteria for Long COVID?

Q2 PREVALENCE-What are the latest estimates of the proportion of those infected who go on to develop Long COVID, in its various forms, with a particular focus on those experiencing long-term, debilitating symptoms? Could we unpick some of the differences between estimates, prevalence by symptom or syndrome, and the impact on people's ability to work, care, study, etc.?

Q4 DEMOGRAPHICS- What is the distribution of Long COVID by age, sex, deprivation, ethnicity, occupation etc.?

Q5 DEMOGRAPHICS- What is the specific risk to children?

Q6 VACCINES-What do we know so far about vaccine effectiveness against Long COVID and how does this shape the risk for future waves?

Q11 RISK FACTORS- What might the longer term risks, including comorbidities, be for sufferers of Long COVID (including for younger people and children)?

Executive Summary

Long COVID symptom prevalence at 12 weeks post SARS-CoV-2 infection is uncertain and estimates vary by study design, ranging from 2.3%-37% in those infected [Medium Confidence]. The proportion reporting symptoms limiting daily living range from 1.2% in young adults, to 4.8% in middle age [High Confidence]. Trends in long COVID lag but map to those for COVID-19 infections [High Confidence]. Fatigue is the most frequently reported persistent long COVID symptom [High Confidence]. No clear individual syndromes have yet been identified [Medium Confidence]. Consistent risk factors across studies include increasing age, female sex, overweight/obesity, pre-existing asthma, pre-pandemic poor physical and mental health, and hospitalisation for initial infection [High Confidence]. Evidence of long COVID prevalence specifically in school-aged children is limited and existing studies are small; published estimates suggest that it does occur but is uncommon, 25 (1.8%) of 1,379 children (all ages) experienced symptoms for ≥ 56 days [Medium Confidence]. Risk of Long COVID may be reduced in individuals who become infected after double vaccination compared to those not vaccinated; however, published evidence is limited to small observational studies, which may be subject to bias [Medium Confidence]. Rates of medium-long term multi-organ sequelae (respiratory disease, major adverse cardiovascular event, diabetes, renal failure, and liver disease) are elevated in patients hospitalised with COVID-19 compared with matched general population but are similar to those hospitalised with pneumonia; however, estimates of the incidence of post-infection adverse events in non-hospitalised COVID-19 cases are lacking [High Confidence].

Q1 and Q2: DEFINITION AND PREVALENCE

Q1- DEFINITION - How can we define Long COVID, disaggregating the various syndromes from each other? What are the clinical diagnostic criteria for Long COVID?

Q2- PREVALENCE-What are the latest estimates of the proportion of those infected who go on to develop Long COVID, in its various forms, with a particular focus on those experiencing long-term, debilitating symptoms? Could we unpick some of the differences between estimates, prevalence by symptom or syndrome, and the impact on people's ability to work, care, study, etc.?

Summary: Fatigue is the most frequently reported persistent symptom [High Confidence]. Evidence for distinct clusters remains unclear [Medium Confidence]. In surveys of test-confirmed and/or suspected COVID-19 cases, proportions self-reporting long COVID vary substantially due to:

- Choice, number, and timing of symptom reporting used to define long COVID
- Cut point for duration of symptoms (>4 or >12 weeks)
- Heterogeneity of study samples and study methods
- Any symptoms versus symptoms severe enough to impact daily living
- Any symptoms versus symptoms attributable to COVID-19

Prevalence of long COVID in those infected

Estimates of the prevalence of symptoms at 12 weeks post confirmed or suspected SARS-CoV-2 infection range from 2.3% from the COVID Symptom Study App [1] to 37.7% from REACT-2 [2]. Experimental ONS research suggests prevalence 13.7% at 12 weeks [Medium Confidence], [3] though the methodology behind this is currently being refined.

When considering only debilitating symptoms, estimates at 12 weeks post infection ranged from 1.2% of 20 year old cases to 4.8% of 60 year old cases (CONVALESCENCE [4]) [High Confidence].

Unsurprisingly, hospitalised patients report greater levels of persistent, debilitating symptoms: for example, 19% changed occupational status at 5 months post-discharge in one study (PHOSP-COVID).[5]

Compared to the proportions of persistent symptoms observed in surveys, long COVID reporting in primary care electronic health records (EHR) is considerably lower [4]. Among individuals with any acute COVID-19 diagnostic code in one database of EHR from England, 0.3% had a long COVID diagnostic code. However, reporting in this resource was 2-3 times lower than in EHR from a different primary care IT provider, and clearly current estimates from EHR should be treated with caution and evaluated further as coding practices improve over time.

Population prevalence of long COVID

Estimates of the number of people in the UK population suffering from long COVID symptoms vary from ~1 million with symptoms for 4+ weeks in the UK (ONS-CIS [6]) to 2 million adults with symptoms for 12+ weeks in England alone (REACT [2]). The CIS produces serial point-in-time prevalence estimates (most recently, self-reported long COVID at 6 June 2021), whereas the REACT-2 estimate reflects period prevalence (ever experienced persistent symptoms by 8 Feb 2021). The REACT-2 estimate therefore may include people who have recovered from their symptoms by 6 June 2021, who will not be included in the ONS estimate. Many other differences in long COVID

definition, questionnaire routing, presentation of questions, and study methodology could also have contributed to the variation between these estimates (see Table 1). Also of note, these estimates both reflect enduring symptoms of any severity, not necessarily proportions of individuals that regarded symptoms to be debilitating. In the latest CIS data, 65.9% of the individuals classified as having long COVID reported at least some limitation of day-to-day activities. REACT-2 did not collect data on whether respondents felt enduring symptoms affected daily living.

Across the spectrum of persistent symptoms observed in COVID-19 cases, persistent fatigue is the most frequently reported symptom [High Confidence]. Others commonly reported include weakness, muscle and joint pains, shortness of breath, poor concentration ('brain fog') and disturbed sleep. Analysis of symptom clustering remains incomplete. [6]

Full details of the studies are summarised in **Table 1**.

Possible reasons for differences between prevalence estimates

Many factors will have contributed to differences in proportions observed between studies including questionnaire design, population characteristics, representativeness, the regions of sampling, and timing of sampling.

Difference in question wording: In the two major studies that have estimated overall prevalence of long COVID nationwide, the ONS CIS asks "would you describe yourself as having 'long COVID'?", whereas REACT-2 asks "which of the following symptoms were part of your COVID-19 illness?" The CIS is potentially more liable to false-negatives (people who really do have persistent symptoms following COVID-19 but do not recognise themselves as having "long COVID"), which may be particularly true among asymptomatic infections who never received a test. Both studies are also liable to false-positives (people who are experiencing symptoms, but not as the result of coronavirus infection), but REACT-2 is arguably more so, particularly as some of the 31 symptoms included in the questionnaire (e.g. runny nose, sneezing) are likely to be reasonably common in the population at any given time. This is a trade-off, and neither definition is obviously superior or inferior to the other. The REACT-2 questionnaire also asks for the (approximate) date when symptoms ended if they haven't already done so, so could be liable to recall bias, as the authors acknowledge in the preprint.[2]

Difference in question routing: All CIS participants are asked the long COVID question, including those who have previously tested positive for coronavirus but were asymptomatic at the acute phase. Conversely, only REACT-2 participants who self-reported COVID-19 (by definition, only those with symptomatic illness) were asked about persistent symptoms. All else being equal, we would therefore expect the REACT-2 estimate to be higher than that from the CIS if the presence of symptoms at the acute phase is a risk factor for experiencing long COVID.

Difference in Long COVID Severity: In CONVALESCENCE, participating longitudinal studies principally defined long COVID in one of two ways. A more inclusive long COVID definition used by some studies asked respondents categorically, *without querying the severity of the persistent symptoms*. Another set of studies used a more stringent long COVID definition that required respondents to indicate that symptoms persisting for 4+ or 12+ weeks *led to some degree of impediment to daily activity*.

Ascertainment of symptoms in populations without COVID: The CONVALESCENCE study, the COVID Symptoms Study and the ONS Coronavirus Infection Survey were the only studies that compared

symptom reporting in the population which did not report COVID-19. In CONVALESCENCE, using a symptom counting approach, proportions of COVID-19 cases reporting symptoms over 12+ weeks ranged between 40.9-45.6%.[4] High proportions were also found in those who had not had COVID-19 with this ascertainment method (12+ weeks, 28.8%). In contrast, the ONS study compared persistent symptoms lasting 12+ weeks using a survival analysis approach between confirmed COVID-19 cases and age- and sex-matched non-COVID controls, with estimates of 13.7% in cases and just 1.7% in controls.

Prospective versus retrospective data collection: Prospective data collection on ongoing symptoms on a daily basis was uniquely performed in the COVID Symptoms Study, which had the lowest estimates of proportions of cases affected, (2.3% for >12 weeks symptoms).[1] Unpublished analysis of the same individuals asked retrospectively about symptoms using the same questionnaire as in CONVALESCENCE cohorts (inclusive method) revealed very similar proportions with symptoms lasting >12 weeks, ranging from 6% of COVID+ cases in men aged 20-30 to 16% in women aged 40-50. The COVID Symptoms Study did not count symptoms re-emerging after a week of reporting no symptoms, but although relapse rates were higher in the case population (16.0%) versus non-COVID controls (8.4%; $P < 0.0005$), this does not account for the difference in reporting rates and suggests that recall bias may operate in retrospective self-reports of symptom duration. The ONS study of persistent symptoms in confirmed infections was based on prospective data [3](symptoms experienced in the last week, collected each week for the month from enrolment and then each month for up to a year); whereas symptom durations for the population prevalence estimate [6] is based on retrospective reporting of the initial (confirmed or suspected) infection.

Table 1. Comparison of Long COVID (LC) study methods and results

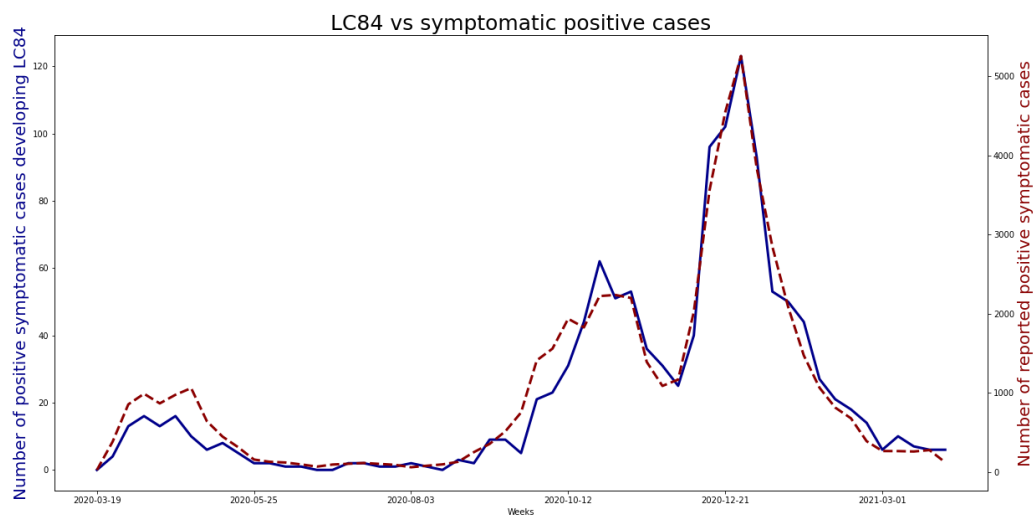
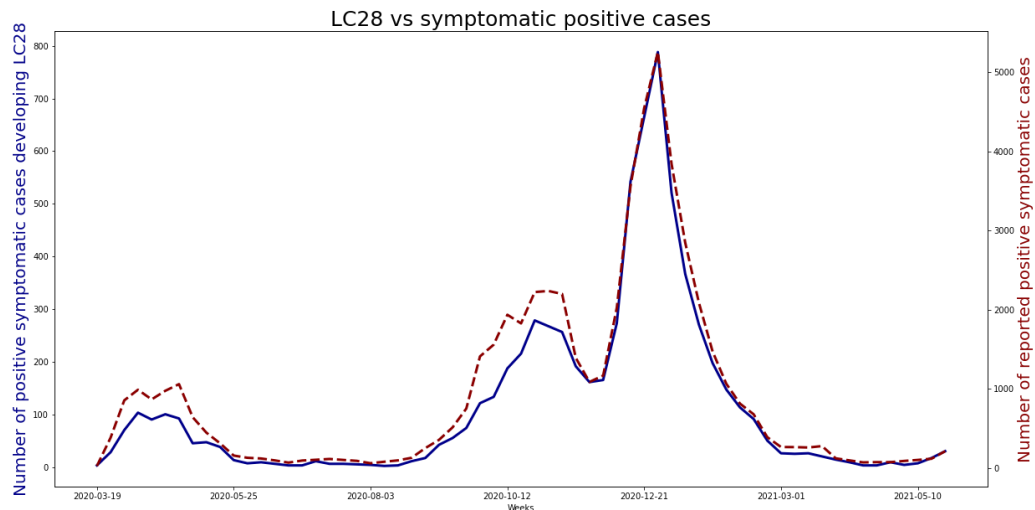
	ONS-CIS [3][6]	REACT-2 [2]	CONVALESCENCE (LHW National Core Study)[4]		COVID Symptom Study [1]
Leading Department/ University	ONS, DHSC, PHE, Wellcome Trust, Oxford, and Manchester	Imperial College London	University College London (Many other Institutions)	University College London, Bristol, and Oxford.	Kings College London
Study population	All individuals aged 2+ years in randomly selected private households (n=528,931)	Randomly selected from the community (n=508,707)	10 population-based longitudinal cohorts (n=45,096)	Primary Care electronic health records (n=1.1 million)	Adults and children with the app (n=4,681,542)
Suspected/ confirmed COVID-19	Population prevalence: 313,216 suspected/ confirmed infections. Prevalence in those infected: 21,622 (confirmed)	92,116 (19.2%)	6907 (14.1%)	1.07 million	4,182
LC Symptom Reporting	Population prevalence: self-reported >4w and >12w, and daily ability limited. Prevalence in those infected: at least one of 12 persistent symptoms	Self-reported persistent 1 and 3+ symptoms >12w	Self-reported persistent symptoms that affect daily life attributed to COVID-19, >4w and >12w	GP coded LC	Prospectively collected self-reported symptoms continuing for >4, >8 and >12w, in participants healthy before positive for SARS CoV2. Relapses after >7 days not counted.
LC prevalence	962,000 people aged >2y (England 6.6.21)	2 million people >18y (England 8.2.21)	N/A	N/A	N/A
LC proportion of study population	1.5% (4w), 1.3% (12w), 1.0% daily activity limited	N/A	N/A	N/A	N/A

	ONS-CIS [3][6]	REACT-2 [2]	CONVALESCENCE (LHW National Core Study)[4]		COVID Symptom Study [1]
LC proportion of those +ve for COVID-19	21.0% 5w 13.7% 12w	5.75% (1 symptom) 2.22% (3+ symptoms)	18% (4w) 1.2-5.4% (12w) daily life affected	0.3%	13.3% (4w) 4.5% (8w) 2.3% (12w)
Demographics linked to reported LC Symptoms	35-69 years old, female sex, living in deprived areas, other health conditions and disabilities, white ethnicity.	Increasing age, female sex, obesity, lower income, smoking/vaping, occupation (health and Care home workers), non-Asian ethnicity.	Increasing age (up to 70y), female sex, white ethnicity, pre-existing asthma, poor physical and mental pre-pandemic health.		Increasing age, female sex, increased body mass.
Time of estimates	Point in time	Period Prevalence	Time of Survey for each cohort	Point in time	Prospectively collected real-time reporting at least weekly
Asked if LC symptoms are debilitating	Population prevalence: yes Prevalence in those infected: no	No (asked about COVID-19, not LC)	Yes	N/A	No
Adjusted for pre-pandemic health	No	No	Yes	N/A	No, although pre-pandemic health was ascertained and used in models
Whole Population	Yes	No, England only	Yes	No, England only	No
LC question asked in survey	Population prevalence: would you describe yourself as having LC? Prevalence in those infected: have you had any of these 12 symptoms in the last 7 days?	Which of the following symptoms were part of your COVID-19 illness?	Varied by cohort	N/A	Questions on 28 symptoms

The extent to which Long COVID prevalence is following COVID-19 cases (unpublished)

Population prevalence trends in long COVID map those of COVID-19 itself. The COVID-19 Symptom Study continuously captures symptoms from a longitudinal volunteer panel till 8th July 2021.

Figure 1 shows numbers reporting a positive COVID-19 test (red dashed line) for each week, together with the number of cases from that week going on to experience persistent symptoms (blue line) at: ≥ 28 days (LC28) and ≥ 12 weeks (LC84).

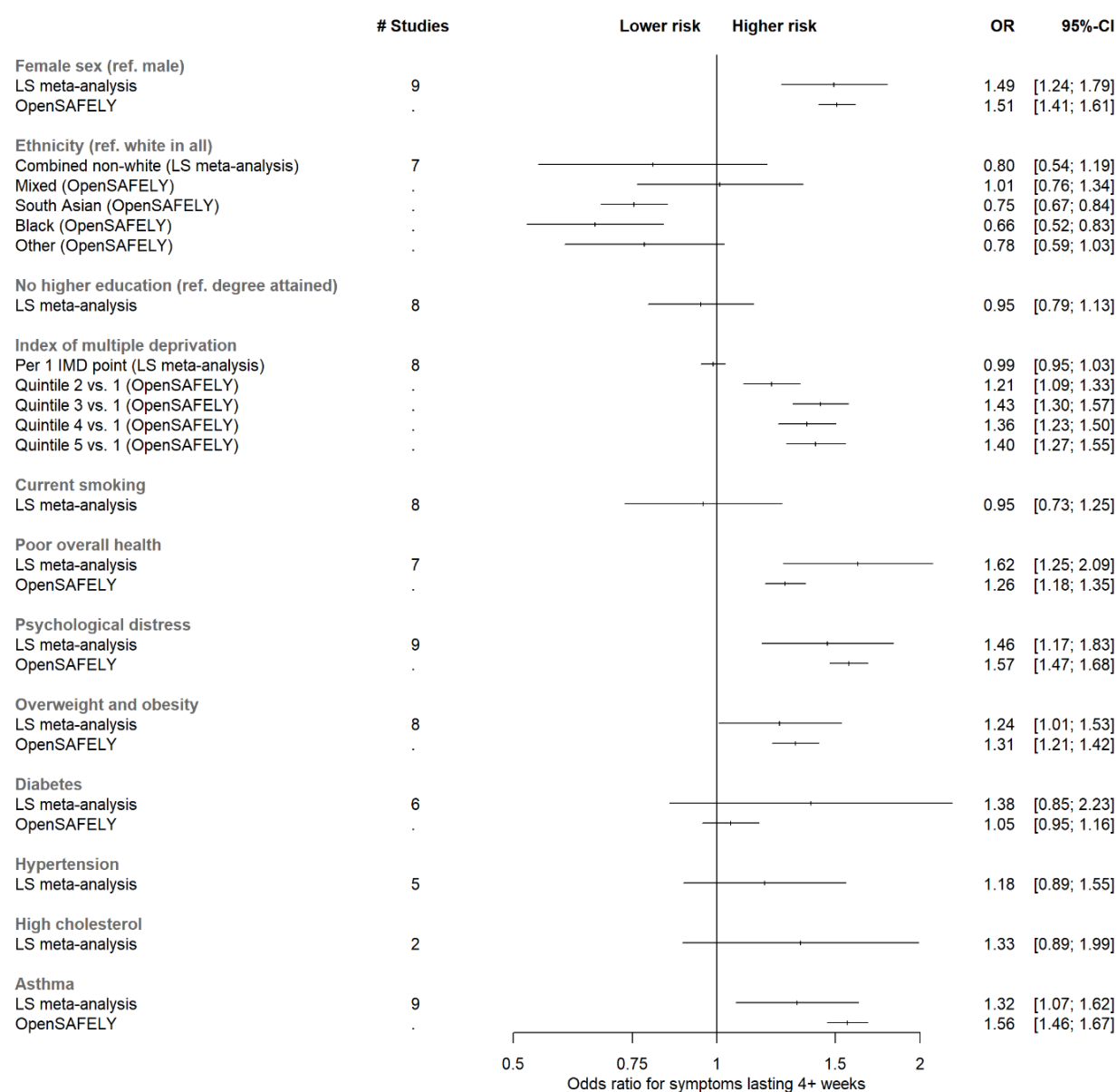


Q4-DEMOGRAPHICS

What is the distribution of Long COVID by age, sex, deprivation, ethnicity, occupation etc.?

Consistent demographic risk factor findings across studies include increasing age, female sex, overweight/obesity, pre-existing asthma, and pre-pandemic poor physical and mental health[1, 2, 4-6]. Non-white ethnic minority groups are less likely to report long COVID. Health and social care workers report greater levels of long COVID, this is largely explained by other (non-employment) socio-demographic characteristics and the risk of initial infection. [7] Those hospitalised with COVID have greater risks of long COVID. Results for deprivation are inconsistent, showing greater risks with both affluence and deprivation [High Confidence].

Figure 2 Risk factors associated with long COVID from meta-analyses of Longitudinal Studies findings alongside corresponding analyses from EHRs [4]



Q5- DEMOGRAPHICS**What is the specific risk to children?**

ONS estimates of the UK population prevalence of self-reported long COVID in children at 6th June 2021 are presented below in Table 2.

Table 2: UK population prevalence of self-reported long COVID (any severity) in children aged ≤16 years, with 95% confidence intervals

Age group	Number (thousands)		Percentage of the population	
	≥4 weeks	≥12 weeks	≥4 weeks	≥12 weeks
2 to 11 years	13 (8-18)	10 (5-14)	0.16 (0.10-0.23)	0.12 (0.06-0.17)
12 to 16 years	20 (15-24)	16 (12-20)	0.51 (0.39-0.63)	0.41 (0.30-0.51)

Data from 258,790 children aged 5-17 years were reported by an adult proxy for the COVID Symptom Study between 24 March 2020 and 22 February 2021. [8] 1,734 children (588 younger, 1,146 older children) had a positive SARS-CoV-2 test result and calculable illness duration within the study time frame. Seventy-seven children (4.4% of those infected) had illness duration ≥28 days (LC28), more commonly experienced by older (12-17yrs) vs. younger (5-11yrs) children (59 (5.1%) vs. 18 (3.1%), $p=0.046$). 25 (1.8%) of 1,379 children (all ages) experienced symptoms for ≥56 days. The study found that long illness duration after SARS-CoV-2 infection in school-aged children does occur, but was uncommon, with only a small proportion of children experiencing illness duration beyond four weeks; and the symptom burden in these children usually decreased over time. Almost all children had symptom resolution by eight weeks. Additionally, symptom burden in children with long COVID was not greater than symptom burden in children with long illnesses due to causes other than SARS-CoV-2 infection.

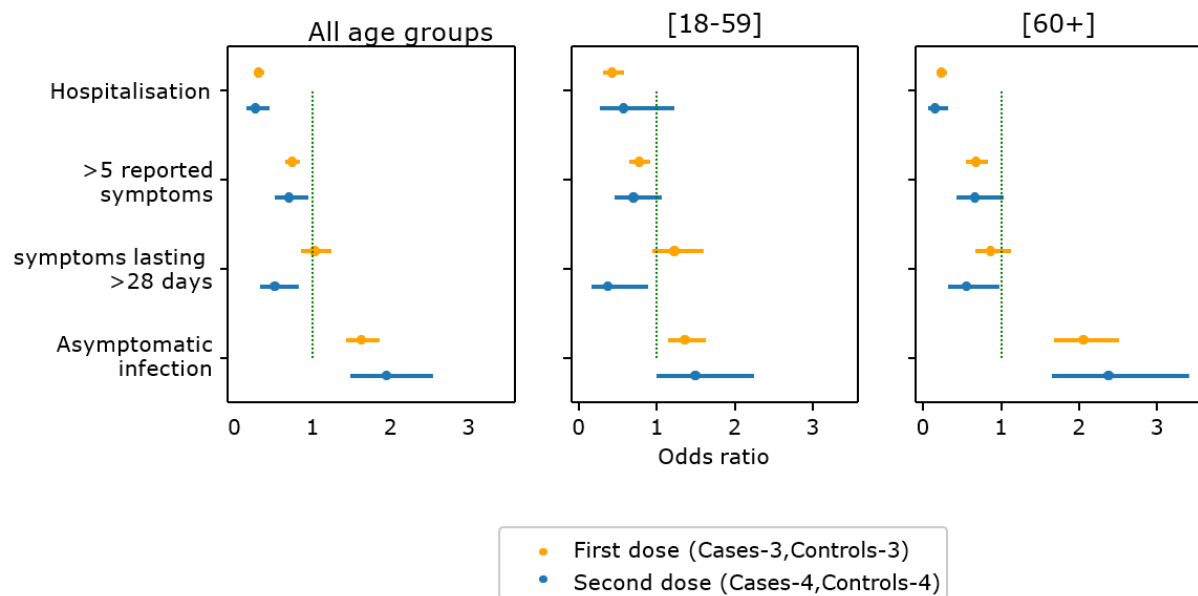
In Zurich, a low prevalence of symptoms compatible with long COVID is reported in a randomly selected cohort of children assessed 6 months after serologic testing [9]. Low numbers of children tested positive (109/1354) from October 2020-April 2021 (6-11 years $n=66$ and 12-16 years $n=43$) and had at least 1 symptom lasting beyond 12 weeks. Similar proportions of seropositive and seronegative children reported excellent or good health. Although long COVID exists in children, estimates of the prevalence of persisting symptoms based on scarce literature range from 0% to 27%. [10]

Q6- VACCINATION**What do we know so far about vaccine effectiveness against Long COVID?**

Illness duration, severity, and symptom profile in adults logging symptoms after SARS-CoV-2 infection contracted >14 days after first ($n=3825$) and >7 days after second vaccinations ($n=906$) were compared to unvaccinated adults with SARS-CoV-2 infection matched by date of positive test, healthcare worker status, sex, BMI, and age (unpublished) .[11]

In all age groups the odds of experiencing symptoms for more than 28 days after post-vaccination infection was approximately halved by two vaccinations. Given that vaccinated individuals have a reduced risk of infection overall, this suggests that risk of Long COVID is substantially reduced in individuals who have received double vaccination.

Figure 3 shows the odds ratio of asymptomatic infection, duration of symptoms ≥ 28 days, severe disease (>5 reported symptoms during acute infection), and hospitalisation in post-vaccination cases compared to matched unvaccinated cases in app participants following first (orange) and second (blue) vaccine dose, adjusted by age, BMI, and sex.



A descriptive analysis of 900 people with long COVID who responded to an online questionnaire posted by the support group LongCOVIDSOS [12], 56.7% of people saw an overall improvement in symptoms following vaccination, 18.7% a deterioration, and 24.6% unchanged. Symptom improvement was more common in respondents who had received an mRNA vaccine.

Observational studies such as those reported above are prone to bias (such as placebo effects) and cannot be used to definitively address the question as to whether vaccine reduces risk of long COVID.

Q11- RISK FACTORS

What might the longer term risks, including comorbidities, be for sufferers of Long COVID?

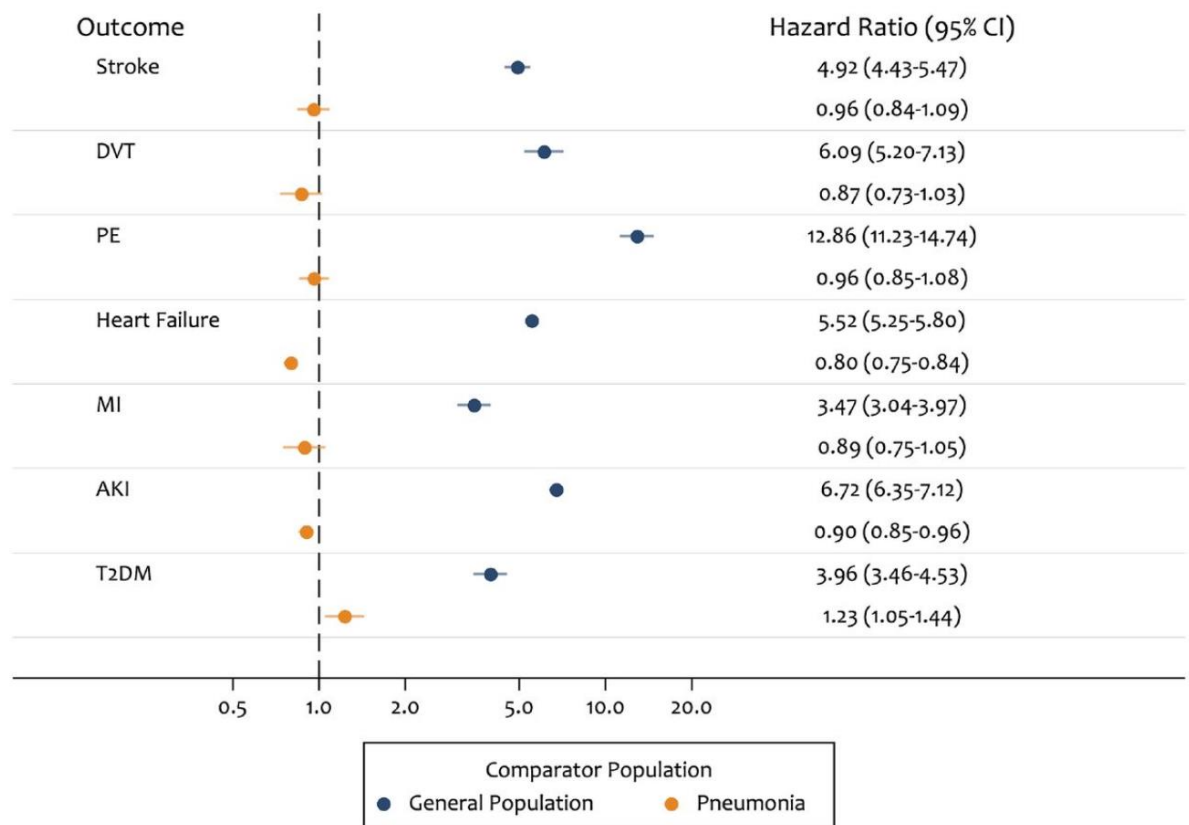
Medium - long term sequelae in those hospitalised

In a study of the EHRs of nearly 50,000 patients discharged alive from hospital following COVID-19, 29.4% were readmitted and 12.3% died within a mean of 140 days post discharge,[13] with rates of multi-organ sequelae (respiratory disease, major adverse cardiovascular event, diabetes, renal failure, and liver disease) being significantly elevated in these patients compared with matched general population. In a separate study using national linked primary care records (OpenSAFELY), hospitalised patients were also found to have markedly increased risk of all major outcomes compared to matched healthy population controls, especially for pulmonary embolism [14]. However, to capture COVID specific sequelae, now using those discharged with pneumonia as controls, there were few differences in major adverse outcomes apart from type 2 diabetes.

There have been reports of subclinical target organ damage, specifically cardiac and brain, as a consequence of COVID infection itself. Further data will be available in ~1-2 years on key target organs (lungs, brain, heart, kidneys), from ongoing imaging studies in both hospitalised patients, and in the general population.

Additionally, over 25% of adults hospitalised with COVID-19 had significant anxiety and depression at five months post-discharge, 17% had significant cognitive impairment using cut-offs typically used for memory clinics. Burden and severity of symptoms is not solely explained by organ damage (or related to severity of acute illness). [5]

Figure 4 demonstrates that cardiometabolic and pulmonary adverse outcomes are markedly raised following hospitalisation for COVID-19 compared to the general population. However, the excess risks were comparable to those seen following hospitalisation with pneumonia.



2. Questions we may be able to answer later

- **DEFINITION AND PREVALENCE (Q1-3)**

Ongoing work on symptom clustering, in relation to risk factors and underlying pathways, is ongoing. Additionally, repeat surveys will provide new estimates of period prevalence, of persistence of, and of recovery from long COVID.

- **DEMOGRAPHICS AND RISK FACTORS (Q4, 5, 11)**

In depth analysis of population cohorts, with detailed pre-pandemic data, and linkage of surveys to health records will enable greater understanding of, key pathways (in cohorts), and co-morbidities (electronic health records) underlying risk of long COVID. In addition, the ONS Coronavirus Infection Survey will investigate viral characteristics, such as viral load, variant, and number/mix of symptoms at the acute phase, as possible predictors of long COVID. The role of vaccination will be explored. Importantly, analysis will take account of selection into COVID caseness (exposure and susceptibility factors), and attrition due to survival bias, to fully understand determinants of long COVID. An important, though challenging analysis, will be to understand determinants of recovery from long COVID.

- **VACCINATION (Q6)**

Like the COVID Symptom Study, other studies (e.g. ONS CIS - reporting August) are exploring the changes in the trajectory of the probability and severity of self-reported long COVID following vaccination. It is important to stress that observational studies cannot wholly reliably replicate a clinical trial.

- **TREATMENTS (Q7)**

Need to identify additional expertise

- **VARIANTS (Q8)**

ONS is exploring the role of variants in long COVID, starting with a basic feasibility assessment of using the CIS (sample sizes may be prohibitive, especially for first wave infections when the study was in its pilot phase). OpenSAFELY and ONS are both in the process of linking COG-UK genomics and national testing data, which would provide population-level data on variants (though obviously data on early variants will still be limited due to the lack of national testing programmes).

- **ROLE OF REINFECTION OR IMPACT OF DE NOVO ARI (Q9)**

As with the above, ONS is exploring the feasibility of assessing reinfection as a risk factor for long COVID, subject to the number of reinfections in the CIS sample.

- **SPECIAL GROUPS (Q10)** e.g. IMMUNOCOMPROMISED

ONS has linked CIS data to primary care and hospital records to explore clinical risk factors for long COVID. Similar analysis could be performed in other national TREs, such as NHS Digital and OpenSAFELY, to correlate comorbidities of interest with diagnosed post-COVID-19 syndrome.

- **IMPACTS (Q12-17)**

Later this month ONS will publish estimates of social impacts (occupation, education, caring, relationships) of long COVID from the Opinions and Lifestyle Survey. Similar analyses are forthcoming from the Longitudinal Health & Wellbeing NCS.

Impacts on children's learning

We are checking with experts but also need to identify additional expertise for SAGE.

The COVID Social Mobility and Opportunities (COSMO) Study aims to address this for year 11 students – it will be some time before data become available.

<https://www.ucl.ac.uk/ioe/departments-and-centres/centres/centre-education-policy-and-equalising-opportunities/research-themes/schools/covid-social-mobility-and-opportunities-study-cosmo>

Demands on NHS and costs

Need to identify additional expertise

Impact on social care

Need to identify additional expertise

Mortality

Ongoing analysis in OpenSAFELY and other national trusted research environments

- **Comparators with SARS and MERS (Q18)**

Need to identify additional expertise

References

1. Sudre, C.H., et al., *Attributes and predictors of long COVID*. Nat Med, 2021. **27**(4): p. 626-631.
2. Whitaker, M., et al., *Persistent symptoms following SARS-CoV-2 infection in a random community sample of 508,707 people*. medRxiv, 2021.
3. ONS, *All data related to Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 1 April 2021*. 2021 April.
4. Thompson, E.J., et al., *Risk factors for long COVID: analyses of 10 longitudinal studies and electronic health records in the UK*. medRxiv, 2021.
5. Evans, R, et al., *Physical, cognitive and mental health impacts of COVID-19 following hospitalisation – a multi-centre prospective cohort study*. medRxiv, 2021.
6. ONS. *Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 1 July 2021*. 2021, July 1; Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/1july2021>.
7. ONS. *Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 1 July 2021*. 2021, June 4; Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/4june2021>.
8. Molteni, E., et al., *Illness duration and symptom profile in a large cohort of symptomatic UK school-aged children tested for SARS-CoV-2*. medRxiv, 2021.
9. Radtke, T., et al., *Long-term Symptoms After SARS-CoV-2 Infection in Children and Adolescents*. Jama, 2021.
10. Say, D., et al., *Post-acute COVID-19 outcomes in children with mild and asymptomatic disease*. Lancet Child Adolesc Health, 2021. **5**(6): p. e22-e23.
11. Antonelli, M., et al., *Post-vaccination SARS-CoV-2 infection: risk factors and illness profile in a prospective, observational community-based case-control study*. medRxiv, 2021.
12. LongCOVIDSOS. *The impact of COVID vaccination on symptoms of Long Covid. An international survey of 900 people with lived experience*. 2021; Available from: https://3ca26cd7-266e-4609-b25f-6f3d1497c4cf.filesusr.com/ugd/8bd4fe_a338597f76bf4279a851a7a4cb0e0a74.pdf.
13. Ayoubkhani, D., et al., *Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study*. Bmj, 2021. **372**: p. n693.
14. The OpenSAFELY Collaborative, *Rates of serious clinical outcomes in survivors of hospitalisation with COVID-19: a descriptive cohort study within the OpenSAFELY platform*. medRxiv, 2021.

Appendix:

Requested questions to be addressed:

1. **DEFINITION** - How can we define Long COVID, disaggregating the various syndromes from each other? What are the clinical diagnostic criteria for Long COVID? How would we expect these to change as research develops? e.g. break down into a number of syndromes.
2. **PREVALENCE**-What are the latest estimates of the proportion of those infected who go on to develop Long COVID, in its various forms, with a particular focus on those experiencing long-term, debilitating symptoms? Could we unpick some of the differences between estimates, prevalence by symptom or syndrome, and the impact on people's ability to work, care, study, etc.?
3. Could we add estimates of Long COVID incidence and prevalence to the outputs of SPI-M's models?
4. **DEMOGRAPHICS**- What is the distribution of Long COVID by age, sex, deprivation, ethnicity, occupation etc.?
5. What is the specific risk to children?
6. **VACCINES**-What do we know so far about vaccine effectiveness against Long COVID and how does this shape the risk for future waves?
7. **TREATMENTS**-What are the current and anticipated treatments that are effective in reducing severity and duration of symptoms?
8. **VARIANTS** Do we know whether Delta carries a higher risk of someone developing Long COVID than earlier variants?
9. **RISK FACTORS** Can Long COVID be made worse by reinfection or (re)infection by another ARI (acute respiratory infection)?
10. Other than the demographics/socioeconomic factors, what other factors determine someone's risk of developing Long COVID in various forms? Such as pre-existing health conditions or immunocompromised/ immunosuppressed groups. Is there a protective effect of vaccines for these groups?
11. What might the longer term risks, including comorbidities, be for sufferers of Long COVID (including for younger people and children)?
12. **IMPACTS**- What is the impact to people's ability to work, and relative risk to key workforces such as transport workers, health and care staff, teachers?
13. What are the estimates of the impacts on children's learning if they have long COVID? Could we have some estimates together before schools reopen?
14. What is the impact on general well-being? Answer now?
15. What is the anticipated demand on and cost to the NHS including in the longer term, and for particular services?
16. What might the impact of long COVID in older adults be for social care provision?
17. Do we have any evidence that mortality is being caused by long COVID?
18. **COMPARATORS**- What can long-term symptoms of previous coronaviruses (e.g SARS and MERS) tell us about Long COVID? To what extent can this be compared to COVID-19?