

1 **Risk of new-onset Long Covid following reinfection with SARS-CoV-2:**
2 **community-based cohort study**

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40 **Abstract**

41 Background: Little is known about the risk of Long Covid following reinfection with
42 SARS-CoV-2. We estimated the likelihood of new-onset, self-reported Long Covid
43 after a second SARS-CoV-2 infection, and compared to a first infection.

44 Methods: We included UK COVID-19 Infection Survey participants who tested
45 positive for SARS-CoV-2 between 1 November 2021 and 8 October 2022. The
46 primary outcome was self-reported Long Covid 12 to 20 weeks after each infection.
47 Separate analyses were performed for those <16 years and ≥16 years. We
48 estimated adjusted odds ratios (aORs) for new-onset Long Covid using logistic
49 regression, comparing second to first infections, controlling for socio-demographic
50 characteristics and calendar date of infection, plus vaccination status in those ≥16
51 years.

52 Results: Overall, Long Covid was reported by those ≥16 years after 4.0% and 2.4%
53 of first and second infections, respectively; the corresponding estimates among
54 those <16 years were 1.0% and 0.6%. The aOR for Long Covid after second
55 compared to first infections was 0.72 (95% confidence interval: 0.63–0.81) for those
56 ≥16 years and 0.93 (0.57–1.53) for those <16 years.

57 Conclusions: The risk of new-onset Long Covid after a second SARS-CoV-2
58 infection is lower than that after a first infection for those ≥16 years, though there is
59 no evidence of a difference in risk for those <16 years. However, there remains
60 some risk of new-onset Long Covid after a second infection, with around 1 in 40 of
61 those ≥16 years and 1 in 165 of those <16 years reporting Long Covid after a second
62 infection.

63 **Introduction**

64 Long Covid describes symptoms such as fatigue, breathlessness, pain, and
65 cognitive impairment that persist for months or years after a SARS-CoV-2 infection.
66 As of 2 January 2023, 2 million people in the United Kingdom (3.1% of the
67 population) were estimated to be experiencing Long Covid, with 1.5 million of these
68 reporting limitations to their daily activities [1]. SARS-CoV-2 reinfection rates
69 increased rapidly following the emergence of the Omicron variant and remain high.
70 More than 90% of reinfections occurred during the period when the Omicron variants
71 were dominant; as of 23 November 2022, the estimated rate of reinfection was 40.6
72 per 100,000 participant days at risk, compared with 11.5 as of 13 December 2021
73 (before Omicron was the dominant variant) [2]. However, there is limited evidence
74 regarding the risk of new-onset Long Covid following SARS-CoV-2 reinfection.

75 Descriptive data from a survey administered by Long Covid patient support groups in
76 the UK suggest that most respondents with Long Covid (89%) developed it after their
77 first SARS-CoV-2 infection [3]. However, this finding is not generalisable to the whole
78 population as the data were collected from social media support groups for people
79 with Long Covid (i.e., a highly self-selecting group). Another study using data from
80 electronic health records suggests that SARS-CoV-2 reinfection increases the risk of
81 post-acute sequelae such as death and organ-specific impairment up to six months
82 post-infection [4]. However, the study sample of US military veterans is unlikely to be
83 representative of the broader population, and the study did not assess common Long
84 Covid symptoms.

85 We therefore investigated the risk of new-onset Long Covid following a second
86 SARS-CoV-2 infection and how this compares with first infections, using data from a
87 large community-based sample selected at random from the UK population.

88 **Methods**

89 *Study data and design*

90 The main data source for this analysis was the UK COVID-19 Infection Survey (CIS,
91 ISRCTN21086382, [https://www.ndm.ox.ac.uk/COVID-19/COVID-19-infection-](https://www.ndm.ox.ac.uk/COVID-19/COVID-19-infection-survey/protocol-and-information-sheets)
92 [survey/protocol-and-information-sheets](https://www.ndm.ox.ac.uk/COVID-19/COVID-19-infection-survey/protocol-and-information-sheets)), run by the Office for National Statistics
93 (ONS) and comprising a sample of over half a million participants randomly selected
94 from the UK community population (excluding communal establishments such as
95 hospitals, care homes, halls of residence, and prisons).

96 Ethical approval was obtained from the South Central Berkshire B Research Ethics
97 Committee (20/SC/0195). At enrolment, participants aged ≥ 16 years provided written
98 consent, including for optional weekly follow-up assessments for one month followed
99 by at least 12 monthly assessments for the majority of participants. Parents and
100 carers provided consent on behalf of those aged 2-15 years, while those aged 10-15
101 years also provided written assent.

102 At each follow-up assessment, all participants answered a survey questionnaire
103 including questions on confirmed/suspected SARS-CoV-2 infections and Long Covid
104 symptoms, and provided a nose-and-throat swab for polymerase chain reaction
105 (PCR) testing.

106 CIS data for participants in England were linked to Pillar 1 (swab testing for SARS-
107 CoV-2 in UK Health Security Agency laboratories and NHS hospitals for those with a
108 clinical need, and health and care workers) and Pillar 2 (swab testing for SARS-CoV-
109 2 in the wider population, through commercial partnerships, either processed in a
110 laboratory or more rapidly via lateral flow device tests) SARS-CoV-2 test results [5].
111 To classify COVID-19 vaccination status and timing for participants in England, we
112 used CIS responses linked to National Immunisation Management System (NIMS)
113 records, with the latter being used when data conflicted. Vaccination information for
114 participants in Wales, Scotland, and Northern Ireland was obtained from CIS
115 responses alone.

116 We included CIS participants who tested positive for SARS-CoV-2 using PCR tests
117 obtained from national testing programmes (participants in England) or during CIS
118 follow-up (all participants), and self-reported positive swab tests (PCR or lateral flow
119 tests) taken outside of the CIS. Among these participants, we identified first and
120 second infections meeting the inclusion criteria (**Figure 1**); for more details see the
121 Supplementary Methods.

122 We then excluded any infections occurring before 1 November 2021. This date was
123 chosen to ensure a reasonable degree of overlap in the calendar date of infection
124 between first and second infection episodes; the fifth percentile of the calendar date
125 distribution was 6 December 2020 for first infections but 13 November 2021 for
126 second infections among those ≥ 16 years; and 10 December 2020 and 20 October
127 2021, respectively, among those < 16 years (**Supplementary Figure 1**).

128 *Exposure*

129 The exposure was a second versus a first SARS-CoV-2 infection, defined by
130 adapting previous methods used for producing official statistics relating to SARS-
131 CoV-2 surveillance in the UK [6, 7]. For more information, see the Supplementary
132 Methods.

133 *Outcome*

134 The primary outcome was new-onset Long Covid of any severity according to the
135 survey question: “Would you describe yourself as having Long Covid, that is, you are
136 still experiencing symptoms more than 4 weeks after you first had COVID-19, that
137 are not explained by something else?” Participants who responded positively to this
138 question were then also asked about the extent to which their symptoms limited their
139 ability to undertake daily activities (a lot, a little, or not at all), and the presence or
140 absence of 21 individual symptoms attributed to Long Covid (the most commonly
141 reported when the survey question was developed [8-10]). The secondary outcome
142 was activity limiting Long Covid (no Long Covid or Long Covid without activity
143 limitation versus activity limited a little or a lot by Long Covid).

144 We considered participants’ first response to these questions 12 to 20 weeks after
145 the date of the first positive swab in each infection episode (the index date).

146 *Covariates*

147 Covariates included socio-demographic characteristics (age, sex, white or non-white
148 ethnicity, area deprivation quintile group, and self-reported pre-existing health
149 conditions), vaccination status, mode of response to the survey at follow-up for Long
150 Covid (digital or face-to-face interview), calendar date of infection (to account for
151 changes in dominant SARS-CoV-2 variant in circulation and other temporal effects),
152 and the number of days from the index date for each infection episode to follow-up
153 for Long Covid.

154 *Statistical methods*

155 Separate analyses were conducted for those ≥ 16 years and < 16 years. We
156 compared study participants’ socio-demographic characteristics at the first and
157 second infection using means for continuous variables and proportions for
158 categorical variables, with absolute standardized differences $\geq 10\%$ indicating a large
159 imbalance between infection episodes [11].

160 We calculated the crude percentage of participants reporting Long Covid 12 to 20
161 weeks after each infection episode to estimate the absolute risk of new-onset Long
162 Covid. We also calculated the prevalence of a range of Long Covid symptoms as the
163 percentage of those ≥ 16 years who reported having Long Covid after each infection.
164 This was not possible for participants < 16 years due to small sample sizes.

165 Adjusted odds ratios (aORs) for Long Covid 12 to 20 weeks post-infection were
166 estimated from binary logistic regression models, comparing second infection
167 episodes to first infection episodes (reference group). For those ≥ 16 years, models
168 were adjusted for all the covariates outlined above. The models for those < 16 years
169 were adjusted for age, sex, calendar date of infection, and the number of days from
170 the index date to Long Covid follow-up due to an insufficient number of events for

171 some levels of the other covariates. We did not adjust for COVID-19 vaccination
172 status in those <16 years because of the high correlation with age and underlying
173 health status; children aged <5 years are not eligible for vaccination in the UK, and
174 uptake has been low among those aged 5 to 11 years (just 5.2% of the population of
175 England in this age group had received two doses of a COVID-19 vaccine by 8
176 October 2022 [12]). All variables were defined at the index date of each infection
177 episode except mode of response, which was defined at the date of the response to
178 the Long Covid question.

179 Continuous variables (age, follow-up time, and calendar date of infection) were
180 modelled as restricted cubic splines, with boundary knots at the 10th and 90th
181 percentiles and an internal knot at the median of the distributions. We tested one to
182 five knots and selected one internal knot as this minimised the Bayesian Information
183 Criterion for the models.

184 As it is possible that the impact of reinfection on the development of new-onset Long
185 Covid varies across different sub-populations, for the primary outcome, we used
186 likelihood ratio tests to test for effect modification of the association between
187 reinfection and new-onset Long Covid, by interacting reinfection with each of the
188 covariates included in the models.

189 All statistical analyses were performed using R version 3.6 software.

190 Results

191 *Description of the study sample*

192 After applying the study inclusion and exclusion criteria (**Figure 1**), the analysis
193 included 126,108 first infections (110,844 in those ≥ 16 years, 15,264 in those < 16
194 years) and 14,539 second infections (11,244 ≥ 16 years, 3,295 < 16 years) occurring
195 between 1 November 2021 and 8 October 2022 (**Table 1**). Median follow-up time
196 from the start of infection to Long Covid response was 102 days (IQR: 92–112) for
197 those ≥ 16 years and 101 days (92–111) for those < 16 years.

198 40.3% of those ≥ 16 years in the first infection episode group had received two or
199 more doses of a COVID-19 vaccine 90 to 179 days before infection. In the second
200 infection episode group, 35.9% had received at least two doses of a COVID-19
201 vaccine 180–269 days before infection. Most of those < 16 years were unvaccinated
202 in both the first (74.2%) and second (70.1%) infection episode groups.

203 Among those ≥ 16 years, the mean age was higher for first infection episodes (53.9
204 years, SD: 16.6 years) than second infection episodes (47.3 years, SD: 15.9 years)
205 and a larger percentage reported having a pre-existing health condition at the first
206 infection episode (17.4%) than the second infection episode (13.4%).

207 *Long Covid in those ≥ 16 years*

208 Long Covid of any severity was reported by 4,381 of those ≥ 16 years after a first
209 infection (prevalence 4.0%; 95% CI 3.8%–4.1%) and 274 (2.4%; 2.2%–2.7%)
210 following a second infection. Activity limiting Long Covid was reported by 3,103 of
211 those ≥ 16 years (2.8%; 2.7%–2.9%) after a first infection, compared with 180 (1.6%;
212 1.4%–1.9%) after a second infection.

213 The most common symptoms among those ≥ 16 years with Long Covid were fatigue
214 (61.6% after a first infection, 57.7% after a second infection); shortness of breath
215 (33.7% and 30.7%, respectively); muscle ache (26.7% and 28.5%, respectively), and
216 difficulty concentrating (26.1% and 34.7%, respectively) (**Figure 2**). The prevalence
217 of neuropsychological symptoms (such as difficulty concentrating, memory loss or
218 confusion, and worry or anxiety) was numerically higher following a second infection.
219 However, small numbers prevented formal statistical testing.

220 The aOR of reporting Long Covid after a second infection compared to a first
221 infection was 0.72 (95% CI 0.63–0.81) for Long Covid of any severity and 0.66
222 (0.57–0.77) for activity limiting Long Covid (**Figure 3**). There was no evidence for
223 effect modification of the association between reinfection and new-onset Long Covid
224 of any severity by age ($p=0.35$), sex ($p=0.17$), ethnicity ($p=0.98$), area deprivation
225 ($p=0.89$), pre-existing health status ($p=0.14$), vaccination status ($p=0.15$), or calendar
226 date of infection ($p=0.29$).

227 *Long Covid in those < 16 years*

228 Long Covid of any severity was reported by 160 of those < 16 years after a first
229 infection (1.0%; 0.9%–1.2%) and 20 (0.6%; 0.4%–0.9%) following a second
230 infection. Activity limiting Long Covid was reported by 87 of those < 16 years (0.6%;

231 0.5%–0.7%) after a first infection, compared with 12 (0.4%; 0.2%–0.6%) after a
232 second infection.

233 The aOR of reporting Long Covid after a second infection compared to a first
234 infection was 0.93 (95% CI 0.57–1.53) for Long Covid of any severity and 0.95
235 (0.50–1.78) for activity limiting Long Covid (**Figure 3**). There was no evidence for
236 effect modification of the association between reinfection and new-onset Long Covid
237 of any severity by age ($p=0.78$) or sex ($p=0.85$). The interaction with calendar date of
238 infection was statistically significant ($p=0.006$). However, wide confidence intervals
239 meant there was a high degree of uncertainty around this finding, and the results
240 should be interpreted with caution (**Supplementary Figure 2**).

241 **Discussion**

242 *Summary of main findings*

243 Relative to a first SARS-CoV-2 infection, the odds of new-onset Long Covid of any
244 severity or activity limiting Long Covid were 28% and 34% lower, respectively,
245 following a second infection in those ≥ 16 years, even after adjusting for vaccination
246 status and other potential confounders. This finding may partly be the result of some
247 degree of protection against Long Covid being conferred by prior infection (assuming
248 persistent symptoms were not present after the first infection), coupled with
249 survivorship effects. That is, people with a greater predisposition to Long Covid (for
250 example, females or those with certain underlying health conditions [13])
251 experiencing persistent symptoms following a first infection, and therefore not being
252 in the sample eligible to experience new-onset Long Covid following a second
253 infection.

254 In those < 16 years, the crude prevalence of new-onset Long Covid was lower
255 following a second infection compared with a first infection, but this difference was
256 not statistically significant after controlling for confounders. However, confidence
257 intervals were wide, reflecting the smaller sample, and compatible with similar
258 reductions to those seen in those ≥ 16 years.

259 *Comparison with other studies*

260 Research into the risk of Long Covid following reinfection with SARS-CoV-2 is
261 scarce. Our findings are consistent with descriptive data from self-selecting
262 respondents collected by Long Covid patient support groups, which suggest that the
263 majority of respondents who have Long Covid developed it after their first infection
264 [3]. However, most participants were unvaccinated when they were first infected, and
265 being vaccinated is associated with a reduced risk of developing Long Covid
266 following SARS-CoV-2 infection [14-16]. In addition, reinfections became more
267 common following the emergence of the Omicron variant [2], and the risk of Long
268 Covid has previously been shown to be lower for infections compatible with the
269 Omicron variants compared with the Delta variant [17, 18]. Importantly, our analysis
270 of a randomly selected community-based cohort shows that the risk of new-onset
271 Long Covid in those ≥ 16 years is lower following a second infection even after
272 adjusting for vaccination status and calendar date of infection (as a proxy for the
273 dominant SARS-CoV-2 variant in circulation at any given time). However, it is
274 important to note that the population prevalence of Long Covid in the UK has
275 remained relatively stable since the emergence of the Omicron variant due to higher
276 infection rates compared with earlier periods in the pandemic [1].

277 Although the risk of new-onset Long Covid in those ≥ 16 years was lower after a
278 second SARS-CoV-2 infection than a first infection, the absolute risk is not
279 negligible; 2.4%, that is around one in 40, of those ≥ 16 years who did not report
280 Long Covid after their first infection went on to do so after a second infection. Other
281 evidence suggests that SARS-CoV-2 reinfection increases risk of post-acute, multi-
282 organ sequelae up to six months after reinfection, compared with a single infection
283 [4]. Our study extends these findings by examining the relationship between

284 reinfection and common Long Covid symptoms. We found that most symptoms
285 reported by those ≥ 16 years with new-onset Long Covid after a second infection
286 were reported at similar levels of prevalence by participants with Long Covid after a
287 first infection. However, there was some descriptive evidence that the prevalence of
288 neuropsychological symptoms (such as difficulty concentrating, memory loss or
289 confusion, and worry or anxiety) was higher among participants reporting new-onset
290 Long Covid after a second infection, compared with those who reported it after a first
291 infection.

292 The aim of our study was to estimate the risk of new-onset Long Covid after
293 reinfection, rather than the incremental risk conferred by reinfection in addition to that
294 from the primary infection. Several studies have shown that previous infection with
295 SARS-CoV-2 is associated with reduced risk of severe disease and hospital
296 admission following reinfection, with the strongest association in those with hybrid
297 immunity from vaccination and prior infection [19-21]. Since the pathophysiology of
298 Long Covid is poorly understood [22], future research should investigate the
299 biological mechanisms underlying the association between previous immunity and
300 the reduction in risk of developing Long Covid observed in this study. This could
301 improve understanding of the pathogenesis of Long Covid and potentially improve
302 therapeutics.

303 *Strengths and limitations*

304 The main strength of the analysis is the use of data from CIS, comprising
305 approximately half a million people randomly sampled from private households to
306 minimise selection bias. CIS participants are routinely tested for SARS-CoV-2, so
307 our study sample included initially asymptomatic as well symptomatic infections. We
308 adjusted for a wide range of factors that may be related to both the risk of reinfection
309 [2] and developing Long Covid [13, 15]. However, the observational nature of the
310 study means that unmeasured confounding may remain, and thus causality cannot
311 be inferred. In particular, we were only able to adjust for age, sex, calendar date, and
312 follow-up time in the analysis of those < 16 years due to limited sample sizes.

313 The routine testing in CIS also means that we can more completely ascertain
314 infection history compared with using results from national testing programmes or
315 self-report alone. We exploited multiple sources of information, including genetic
316 sequencing, S-gene target positivity, and Ct values to distinguish as much as
317 possible between persistent PCR positivity and new infections. However, one
318 limitation is that inevitably some short infections and/or reinfections may have been
319 missed.

320 We excluded participants who were reinfected less than 12 weeks after their first
321 infection or before they had responded to the Long Covid question 12 to 20 weeks
322 after their first infection. Although only a small number of participants ($n=3,542$, 1.2%
323 of the original sample of first infections) were excluded for this reason, this could
324 introduce bias if a shorter duration of first infection is related to the risk of Long
325 Covid. Consequently, the results may not be generalisable to people who are
326 reinfected with short intervals between their first and second infection.

327 Another limitation is that Long Covid status was self-reported, so outcome
328 misclassification is possible. Some participants may have been experiencing
329 symptoms because of a health condition unrelated to COVID-19, while others who
330 did have Long Covid may not have described themselves as such (for example, due
331 to the perceived stigma associated with the condition [23]). Conversely, self-
332 recognition of Long Covid (participants' perception of the change in their own health
333 compared with pre-infection) may be more reliable than electronic health records in
334 some respects, for example due to differences in healthcare-seeking behaviours
335 between socio-demographic groups and Long Covid diagnoses being under-
336 recorded in primary care [24].

337 This analysis only includes infections occurring between 1 November 2021 and 8
338 October 2022. The Omicron COVID-19 variant was first identified in the UK on 27
339 November 2021 [25] and quickly became the main variant in circulation. Most first
340 and second infections in our sample are therefore Omicron infections, and it is
341 unclear whether our findings are representative of infections with other SARS-CoV-2
342 variants.

343 *Conclusions*

344 The risk of new-onset Long Covid after a second SARS-CoV-2 infection is lower than
345 that after a first infection for those ≥ 16 years even after adjusting for vaccination
346 status and variant (using calendar date as a proxy). Although there was no statistical
347 evidence of a difference in risk between first and second infections for those < 16
348 years, there was a large degree of uncertainty around the point estimate, suggesting
349 this finding could be a consequence of lower power in this smaller subgroup. Despite
350 our finding that reinfection carries a lower risk of new-onset Long Covid than a first
351 infection in those ≥ 16 years, there remains some risk of new-onset Long Covid,
352 following around one in forty second infections among those ≥ 16 years. Further
353 research is required to understand whether the risk of Long Covid is reduced with
354 each subsequent infection. This is essential to model the expected future burden of
355 Long Covid on the population.

356 **Notes**

357 *Author contributions*

358 MLB, DA, and BS conceptualised and designed the study. MLB and BS prepared the
359 study data and performed the statistical analysis. All authors contributed to
360 interpretation of the results. MLB and DA were responsible for the first draft of the
361 manuscript. All authors contributed to critical revision of the manuscript and
362 approved the final manuscript.

363 *Patient involvement*

364 MEO and NAA have lived experience of Long Covid.

365 *Data availability*

366 De-identified study data are available to accredited researchers in the ONS Secure
367 Research Service under part 5, chapter 5 of the Digital Economy Act 2017. For
368 further information about accreditation, contact research.support@ons.gov.uk or
369 visit:

370 [https://www.ons.gov.uk/aboutus/whatwedo/statistics/requestingstatistics/approvedre](https://www.ons.gov.uk/aboutus/whatwedo/statistics/requestingstatistics/approvedresearcherscheme)
371 [searcherscheme](https://www.ons.gov.uk/aboutus/whatwedo/statistics/requestingstatistics/approvedresearcherscheme).

372 *Disclaimer*

373 The views expressed are those of the authors and are not necessarily those of the
374 National Health Service, the National Institute for Health Research (NIHR), the
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389 the NIHR Oxford Biomedical Research Centre and is an NIHR Senior Investigator.
390 NAA is a co-investigator on the NIHR-funded STIMULATE-ICP and HI-COVE studies
391 and has contributed in an advisory capacity to WHO and the EU Commission's
392 Expert Panel on effective ways of investing in health meetings in relation to post-
393 COVID-19 condition.

394 *Potential conflicts of interest*

395 All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of
396 Interest and declare: no support from any organisation for the submitted work; and
397 no financial relationships with any organisations that might have an interest in the
398 submitted work in the previous three years. MEO has received Patient Involvement
399 honorarium for speaking at a Long Covid Physio International Forum panel
400 discussion. NAA is a co-investigator on the NIHR-supported research on Long Covid
401 (STIMULATE-ICP and HI-COVE studies), a Long Covid Kids Charity Champion, a
402 Long Covid Support Charity Advisor, and has contributed in an advisory capacity to
403 WHO and EU Commission's Expert Panel on effective ways of investing in health
404 meetings in relation to post-COVID-19 condition.

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Table 1 Characteristics of study participants

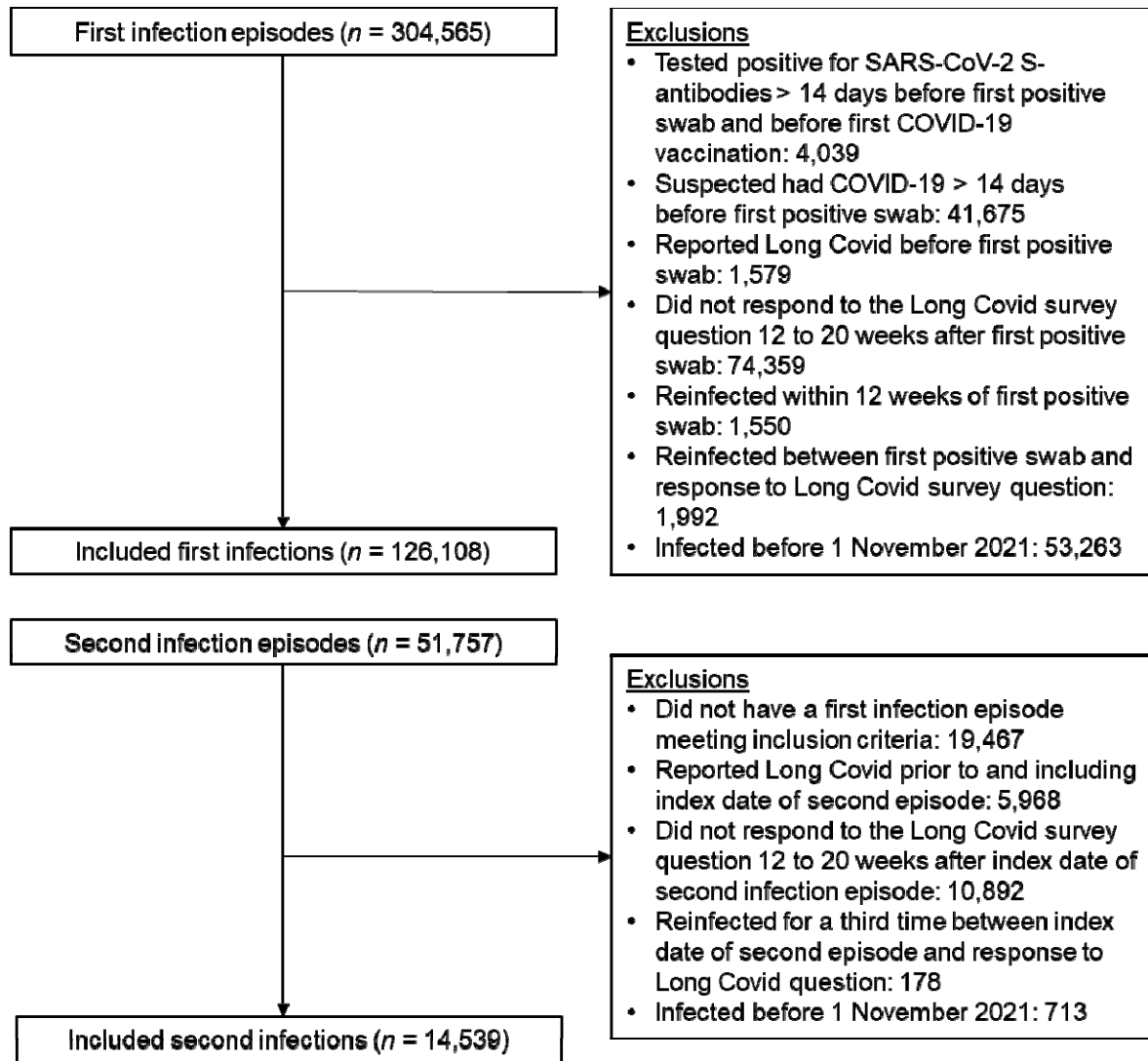
Characteristic ¹	≥16 years at infection			<16 years at infection		
	First infection (n = 110,844)	Second infection (n = 11,244)	Absolute standardised difference (%)	First infection (n = 15,264)	Second infection (n = 3,295)	Absolute standardised difference (%)
Age, years (mean, SD)	53.9 (16.6)	47.3 (15.9)	40.8	9.8 (3.4)	10.5 (3.0)	22.1
Calendar time of infection, number of days since 1 November 2021 (mean, SD)	144.8 (81.8)	189.8 (84.8)	54.0	91.8 (64.1)	165.5 (82.8)	99.5
Number of days from index date to Long Covid follow-up (mean, SD)	103.1 (13.2)	103.1 (12.9)	0.3	102.8 (13.4)	103.2 (13.1)	3.5
Sex (n, %)						
Female	60,572 (54.6)	6,431 (57.2)	5.1	7,484 (49.0)	1,613 (49.0)	0.2
Male	50,272 (45.4)	4,813 (42.8)		7,780 (51.0)	1,682 (51.0)	
Ethnic group (n, %)						
White	104,073 (93.9)	10,253 (91.1)	10.3	13,295 (87.1)	2,836 (86.1)	3.0
Non-white	6,771 (6.1)	991 (8.8)		1,969 (12.9)	459 (13.9)	
Area deprivation quintile group (n, %)						
1 (most deprived)	10,481 (9.5)	1,261 (11.2)	10.7	1,546 (10.1)	388 (11.8)	4.9
2	17,178 (15.5)	2,023 (18.0)		2,312 (15.1)	532 (16.1)	
3	22,983 (20.7)	2,303 (20.5)		3,095 (20.3)	638 (19.4)	
4	27,810 (25.1)	2,644 (23.5)		3,760 (24.6)	776 (23.6)	
5 (least deprived)	32,392 (29.2)	3,013 (26.8)		4,551 (29.8)	961 (29.2)	
Self-reported, pre-existing health conditions (n, %) ²						
No	91,573 (82.6)	9,742 (86.6)	11.2	14,291 (93.6)	3,065 (93.0)	2.4
Yes	19,271 (17.4)	1,502 (13.4)		973 (6.4)	230 (7.0)	
Mode of response to survey (n, %)						
Face-to-face	66,987 (60.4)	4,297 (38.2)	45.6	13,165 (86.2)	1,783 (54.1)	75.0
Digital	43,857 (39.6)	6,947 (61.8)		2,099 (13.8)	1,512 (45.9)	
Vaccination status (n, %) ³						
Unvaccinated	1,545 (1.4)	384 (3.4)	54.7	11,327 (74.2)	2,309 (70.1)	20.0
One dose ≥ 14 days previously	1,197 (1.1)	195 (1.7)		2,561 (16.8)	490 (14.9)	
Two/booster dose ≥ 14 to 89 days previously	28,644 (25.8)	1,998 (17.8)		632 (4.1)	182 (5.5)	
Two/booster dose ≥ 90 to 179 days previously	44,634 (40.3)	3,271 (29.1)		532 (3.5)	230 (7.0)	
Two/booster dose ≥ 180 to 269 days previously	28,362 (25.6)	4,035 (35.9)				
Two/booster dose ≥ 270 days previously	6,462 (5.8)	1,361 (12.1)		212 (1.4)	84 (2.5)	

¹ All characteristics (except mode of response) were defined at index date for each infection episode.

² Obtained from the survey question “Do you have any physical or mental health conditions or illnesses lasting or expected to last 12 months or more, excluding any long-lasting COVID-19 symptoms?”

³ Counts have been aggregated for those <16 years in the two/booster dose ≥ 180 to 269 days previously and ≥ 270 days previously due to small sample sizes. Standardised differences were calculated on the raw counts.

Figure 1: Study participant flow diagram



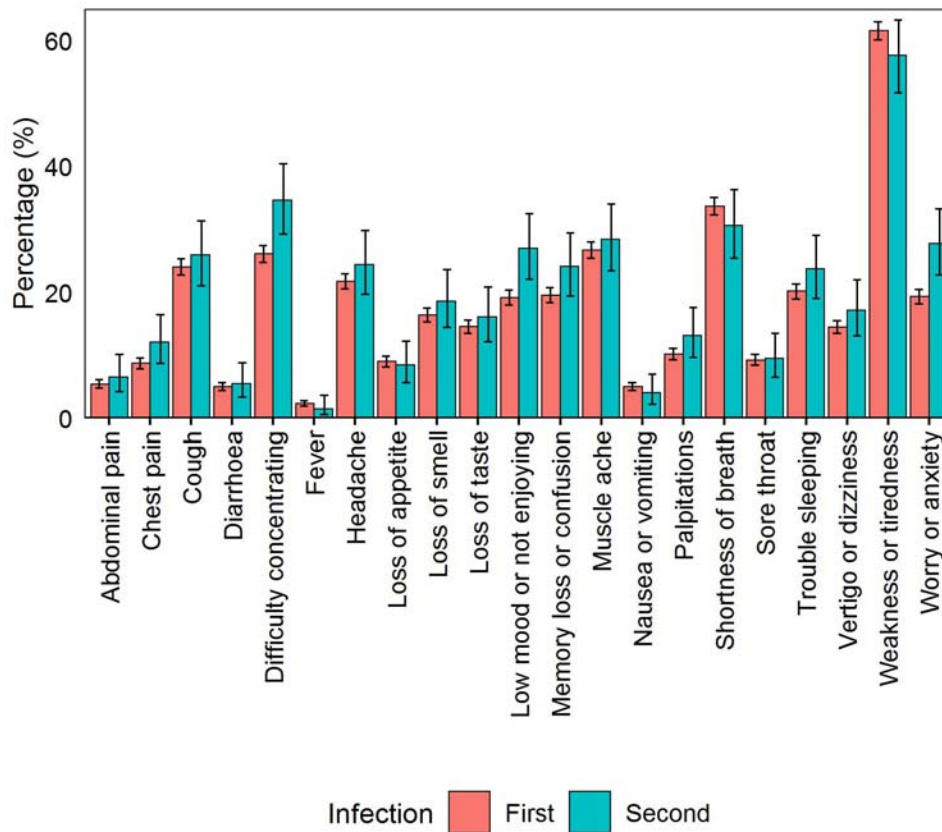


Figure 2. Prevalence of Long Covid symptoms among those ≥ 16 years who reported having Long Covid after a first or second SARS-CoV-2 infection.

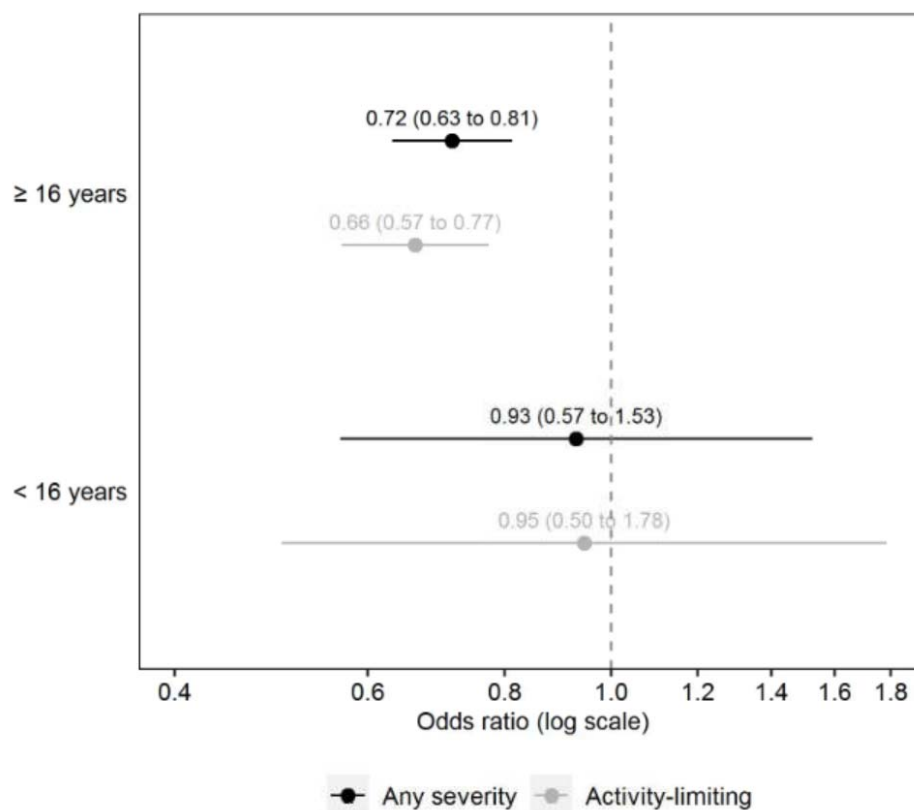


Figure 3. Adjusted odds ratios for Long Covid 12 to 20 weeks after a second SARS-CoV-2 infection compared with a first infection (reference group). Odds ratios for those ≥ 16 years are adjusted for socio-demographic characteristics (age, sex, white or non-white ethnicity, area deprivation quintile group, and self-reported health status), vaccination status, time from infection to follow-up for Long Covid, calendar date of infection (as a proxy for the dominant SARS-CoV-2 variant in circulation), and mode of response to the survey. Odds ratios for those < 16 years are adjusted for age, sex, time from infection to follow-up for Long Covid, and calendar date of infection. Confidence intervals are at the 95% level.

Supplementary Materials

Supplementary Methods

Inclusion & exclusion criteria

To identify first SARS-CoV-2 infection episodes, we excluded participants who reported suspected COVID-19 or tested positive for S-antibodies (in the study or elsewhere, ignoring blood tests taken after first COVID-19 vaccination) >2 weeks before their first positive swab; reported Long Covid symptoms at any time before their first positive swab; did not respond to the survey question on Long Covid 12 to 20 weeks after their first positive swab; or were reinfected within 12 weeks of their first positive swab or before their first response to the Long Covid question 12 to 20 weeks after their first positive swab (since, if these participants experienced Long Covid, it is uncertain whether their symptoms were attributable to the first or second infection).

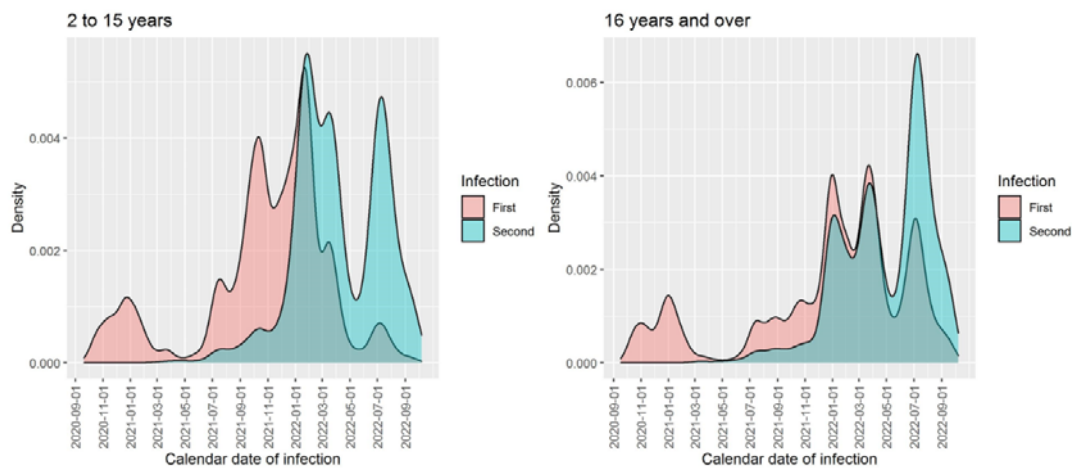
To identify second SARS-CoV-2 infection episodes, we excluded participants with a second episode who did not have a first infection episode meeting the above criteria; reported Long Covid prior to (and including) the start of their second episode; did not respond to the Long Covid question 12 to 20 weeks after the start of their second episode; or were reinfected again before their first response to the Long Covid question 12 to 20 weeks after the start of their second episode.

Exposure definition

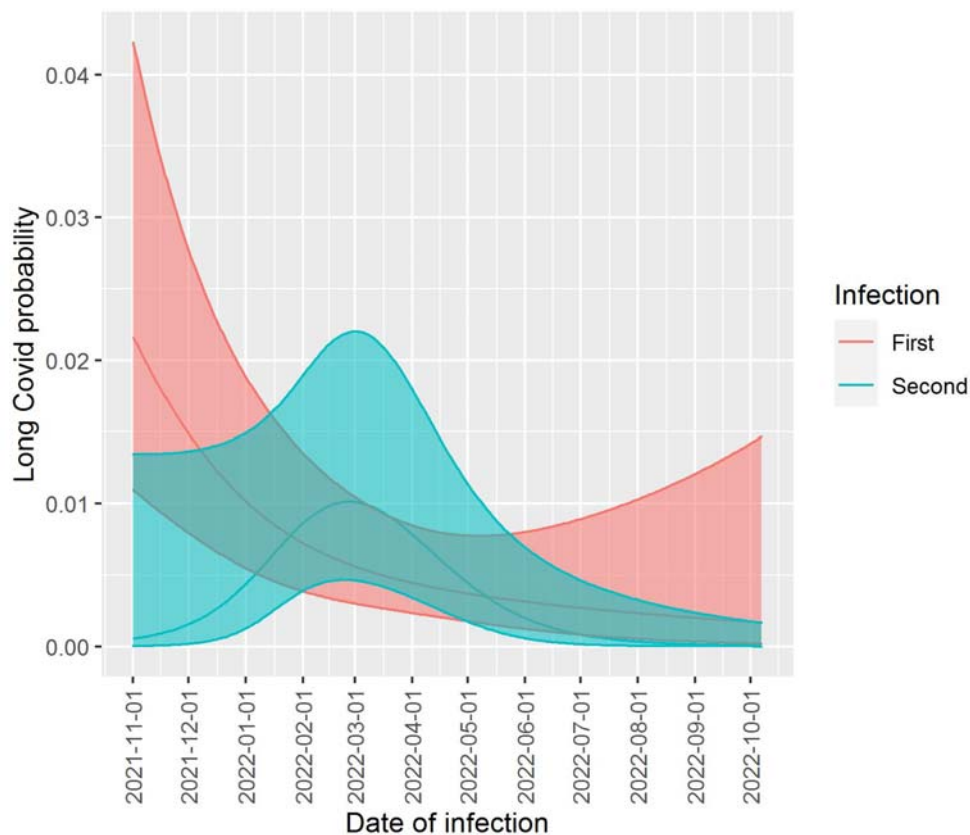
Positive swab test results from any source were grouped into infection episodes to allow for long duration of PCR positivity in some individuals, incorporating information from genetic sequencing, S-gene target positivity and cycle threshold (Ct) values, together with negative PCR test results from CIS only. We defined a new infection episode as a new swab positive occurring >120 days after an index positive with the preceding test being negative, or >90 days with the preceding two consecutive tests being negative (one negative after 20 December 2021 when Omicron variants dominated given higher reinfection rates with Omicron), or >60 days with the three preceding consecutive tests being negative, or after 4 preceding consecutive negative test results at any time.

We further split these infection episodes if they contained multiple sequences from different genetic lineages (e.g., BA.5 and BA.2), or had incompatible S-gene target positivity with Ct<30 (e.g., S-gene positive and S-gene negative, both with Ct<30), or had large decreases in Ct within a set of positive tests grouped together, or low Ct long after the first positive within an episode (both indicative of a new infection rather than ongoing PCR positivity). We also split infection episodes where a new lateral flow device positive was recorded 27 days or more after the start of an infection episode, or 19 days or more after a previous positive PCR or lateral flow test, since this again indicates high viral load and actively replicating virus (more likely associated with a new infection).

Supplementary Figure 1. Density plots of calendar date of infection, stratified by infection episode and age group.



Supplementary Figure 2. Estimated marginal probability of Long Covid by calendar date of infection in those <16 years.¹



¹ Estimates were calculated using the emmeans package, adjusting for age, sex, and time from infection to follow-up for Long Covid. Shaded areas are 95% confidence intervals.