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Long COVID in Children and Young after Infection or Reinfection with the Omicron Variant: A Prospective Observational Study

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To describe the prevalence of long COVID in children infected for the first time (n = 332) or reinfected (n = 243) with Omicron compared with test-negative children (n = 311). Overall, 12%-16% of those infected with Omicron met the research definition of long COVID at 3 and 6 months after infection, with no evidence of difference between cases of first positive and reinfected ($P_{\chi 2}$ = 0.17). *(J Pediatr 2023;259:113463).*

The emergence of the Omicron (B.1.1.529) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in November 2021 was a major change in the pandemic.[1] The variant spread rapidly across the globe, with cases during December 2021 and March 2022 exceeding all previously reported cases.[2] Although Omicron caused less severe acute illness in vaccinated populations compared to previous variants, including in children and young people, its longer-term impact remains relatively unknown.[3] A large case-control study in adults using the National Institute for Health and Care Excellence's long COVID criterion (ie, having symptoms for ≥4 weeks after the start of acute COVID-19) found lower odds of long COVID with Omicron than the Delta variant in the region of 0.24-0.50 depending on age (older adults had greater odds of long COVID) and time since vaccination, corresponding to 4.5% of adults having long COVID after Omicron infection compared to 10.8% after Delta.[2,4] When considering symptoms 12-16 weeks after infection, between 4% and 5% of triple-vaccinated adults self-reported long COVID after infection with either the Omicron or Delta variants.[5]

There is little comparable research regarding the impact of the Omicron variant on long COVID in children and young people The original Children and young people with Long COVID (CLoCk) study, the largest national, matched longitudinal study of long COVID in children and young people, recruited participants aged 11-17 years, who had polymerase chain reaction (PCR) tests between September 2020 and March 2021 in England. These nonhospitalized children and young people self-report on post-COVID-19 health, and PCR-confirmed SARS-CoV-2-positive children and young people are compared with SARS-CoV-2 PCR-negative children and young people. Findings from CLoCk and other studies on earlier variants indicate that, although most children and young people recover well, a minority continue to have impairing symptoms 3 months after infection.[6,7] However, the original CLoCk study was limited by retrospective recall of symptoms at testing and did not include children and young people infected with the Omicron variant.

Given that more than 90% of children and young people have now been exposed to SARs-CoV-2, with large numbers of primary infections and reinfections with Omicron, it is critical to understand the long-term impact of infection: even if a low proportion of children and young people develop long COVID, the scale of Omicron infections and reinfections indicates there could be an unprecedented impact and demand for services.[8] Therefore, our primary objective was to describe the impact of Omicron infection on long COVID in children and young people. Specifically, we aimed to (1) determine the proportion of children and young people meeting the research definition of long COVID at 3 and 6 months across 3 infection status groups: always tested negative (test negative), first SARS-CoV-2 infection during the period when Omicron was dominant (first positive), and previous confirmed SARS-CoV-2 infection with reinfection when Omicron was dominant (reinfected); (2) compare symptom profiles across the 3 groups; and (3) examine differences in long COVID prevalence by age.

COVID	Coronavirus disease
CLoCk	Children & young people with Long COVID
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

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Methods

The CLoCk study methodology has been described elsewhere.[9] For this sub-study, 15 045 CYP who had a PCR test in January 2022 were invited by mail to participate. The first positives were matched at study invitation to the test negatives by age (at last birthday), sex, and geographical area (based on lower super output area) using the national SARS-CoV-2 testing database held at the UK Health Security Agency; all reinfected children and young people were invited (**Figure 1**). Consenting children and young people filled in an online questionnaire at 0, 3, and 6 months after testing. The questionnaires included demographics, elements of the International Severe Acute Respiratory and Emerging Infection Consortium questionnaire, 28 symptoms (eg, shortness of breath, tiredness, brain fog), as well as validated scales including the EQ-5D-Y (which measures health-related quality of life).[10] The Delphi research definition of long COVID in children and young people was operationalized as experiencing 1 or more symptoms and problems with mobility, self-care, doing usual activities, or having pain or discomfort or feeling very worried or sad, based on the EQ-5D-Y scale, at the time of questionnaire completion 3 and 6 months after testing.[11] Children and young meeting this operationalized research definition were classified as having long COVID.

We generated stacked bar charts showing the distribution of (i) individual symptoms at 0, 3, and 6 months (for 26 symptoms; runny nose and sneezing were added in to the 3- and 6-month questionnaires) and (ii) long COVID at 3 and 6 months by the 3 infection status groups, indicating when the symptom/long COVID was first reported. Using χ^2 tests, we assessed whether long COVID varied by age-group (11-14 vs 15-17, based on education key stage groups in England), for each infection status group.

Results

There were 332 first-positive, 243 reinfected, and 311 test-negative children and young people who filled in the online questionnaires at 0, 3, and 6 months after testing and were included in the analytic sample, representing 5.9% of those invited (886/15 089). The analytical sample consisted of

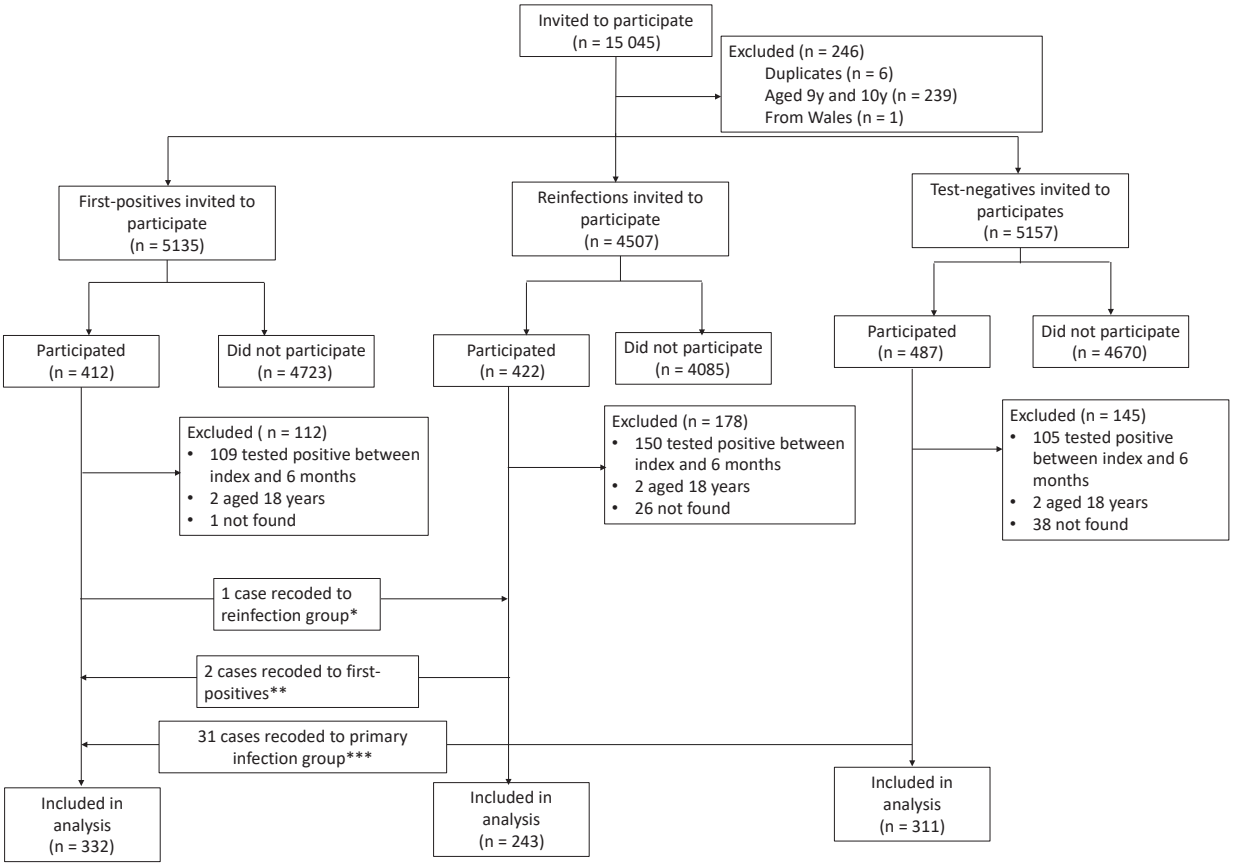

Figure 1. Participant flow diagram.

more females and was older and more affluent than the target sample (Table). There were also some regional disparities; for example, compared with the target, the analytic sample overrepresented South-west England and underrepresented North-west England. By 6 months, 3.8% (34/886) of the included children and young people reported seeking help from general practitioners (family physicians) and 6 children and young people (2 first positive, 3 reinfected, 1 test negative) had stayed overnight in hospital because of COVID-19-related problems (either acute or more long term). The proportion of children and young meeting the long COVID research definition at both 3 months and 6 months was 12.1% (first positives), 16.1% (reinfected), and 4.8% (always tested negative). The Delphi research definition of long COVID in children and young people requires a positive laboratory confirmation of SARS-CoV-2 infection.[11] We excluded the need for a positive PCR test for the 'always tested negative' group to determine how many met this long COVID definition.[11] Although the prevalence of long COVID at both 3 months and 6 months differed by infection status ($P_{\chi 2} < .001$), there was no evidence of difference between first positives and reinfected ($P_{\chi 2} = .17$). Thirteen percent of the reinfected group (ie, those who tested positive previously) met the long COVID definition at baseline (32/243); of these, 41% (13/32) had long COVID at both 3 and 6 months.

Of the 26 symptoms reported at 0, 3, and 6 months, tiredness was consistently the most commonly reported symptom across the 3 infection status groups (Figures 2-4): for example, at 6 months the overall prevalence of tiredness was 33.1% (first positives), 37.0% (reinfected), and 20.9% (test negatives). Examining within-individual variation in symptoms, it was not the case that the specific symptom was consistently reported by the same children and young at 0, 3, and 6 months. Instead, the prevalence of specific symptoms being reported by the same children and young declined from time of testing to 3 months and then declined further or remained stable at 6 months; simultaneously, those same symptoms were reported for the first time by a new cohort of children and young at 3 months and again another new cohort of children and young people first reported the symptom at 6 months (see Figure 5 for an illustration with respect to tiredness). Therefore, across the groups, although the

Table. Demographics of target population and participants included in the analytical sample

	First positive SARS-CoV-2 test		Reinfections SARS-CoV-2 test		Always negative SARS-CoV-2 test	
	Target Population	Study Participants	Target Population	Study Participants	Target Population	Study Participants
Characteristics	(n = 5135)	(n = 332)	(n = 4507)	(n = 243)	(n = 5157)	(n = 311)
Percent of target population		6.47		5.39		6.03
Sex						
Female	2569 (50.03)	193 (58.13)	2217 (49.18)	145 (59.67)	2560 (49.64)	177 (56.91)
Male	2566 (49.97)	139 (41.87)	2280 (50.60)	98 (40.33)	2566 (49.76)	134 (43.09)
Not known	0 (0.00)		10 (0.22)		31 (0.60)	
Age (years)						
11-14	2608 (50.79)	143 (43.07)	3745 (83.10)	179 (73.66)	2666 (51.70)	152 (48.87)
15-17	2527 (49.21)	189 (56.93)	762 (16.90)	64 (26.34)	2491 (48.30)	159 (51.13)
Ethnicity	Not recorded		Not recorded		Not recorded	
White		271 (81.63)		204 (83.95)		259 (83.28)
Asian, Asian British		29 (8.73)		19 (7.82)		31 (9.97)
Mixed		14 (4.22)		11 (4.53)		8 (2.57)
Black, African, Caribbean		11 (3.31)		6 (2.47)		9 (2.89)
Other		3 (0.90)		2 (0.82)		3 (0.96)
Prefer not to say		4 (1.20)		1 (0.41)		1 (0.32)
Region						
East Midlands	570 (11.10)	36 (10.84)	411 (9.12)	22 (9.05)	577 (11.19)	33 (10.61)
East of England	570 (11.10)	34 (10.24)	636 (14.11)	32 (13.17)	574 (11.13)	36 (11.58)
London	570 (11.10)	35 (10.54)	361 (8.01)	14 (5.76)	568 (11.01)	32 (10.29)
North East England	570 (11.10)	32 (9.64)	296 (6.57)	20 (8.23)	570 (11.05)	30 (9.65)
North West England	570 (11.10)	24 (7.23)	499 (11.07)	25 (10.29)	571 (11.07)	30 (9.65)
South East England	570 (11.10)	42 (12.65)	889 (19.72)	49 (20.16)	574 (11.13)	41 (13.18)
South West England	570 (11.10)	48 (14.46)	350 (7.76)	27 (11.11)	573 (11.11)	40 (12.86)
West Midlands	570 (11.10)	38 (11.45)	619 (13.75)	28 (11.52)	568 (11.01)	41 (13.18)
Yorkshire and the Humber	570 (11.10)	43 (12.95)	445 (9.87)	26 (10.70)	571 (11.07)	28 (9.00)
Not Known	5 (0.10)		1 (0.02)		11 (0.21)	
IMD quintile						
1 (most deprived)	1200 (23.37)	54 (16.27)	1053 (23.38)	31 (12.76)	1079 (20.92)	42 (13.50)
2	964 (18.77)	51 (15.36)	800 (17.75)	38 (15.64)	926 (17.96)	40 (12.86)
3	928 (18.07)	56 (16.87)	832 (18.46)	42 (17.28)	963 (18.67)	54 (17.36)
4	988 (19.24)	79 (23.80)	800 (17.75)	62 (25.51)	1002 (19.43)	82 (26.37)
5 (least deprived)	1055 (20.55)	92 (27.71)	1022 (22.67)	70 (28.81)	1187 (23.02)	93 (29.90)

IMD, Index of Multiple Deprivation, calculated from the children and young people's small local area level based geographic hierarchy (lower super output area) at the time of the questionnaire and used as a proxy for socioeconomic status. We report IMD quintiles from most (quintile 1) to least (quintile 5) deprived.

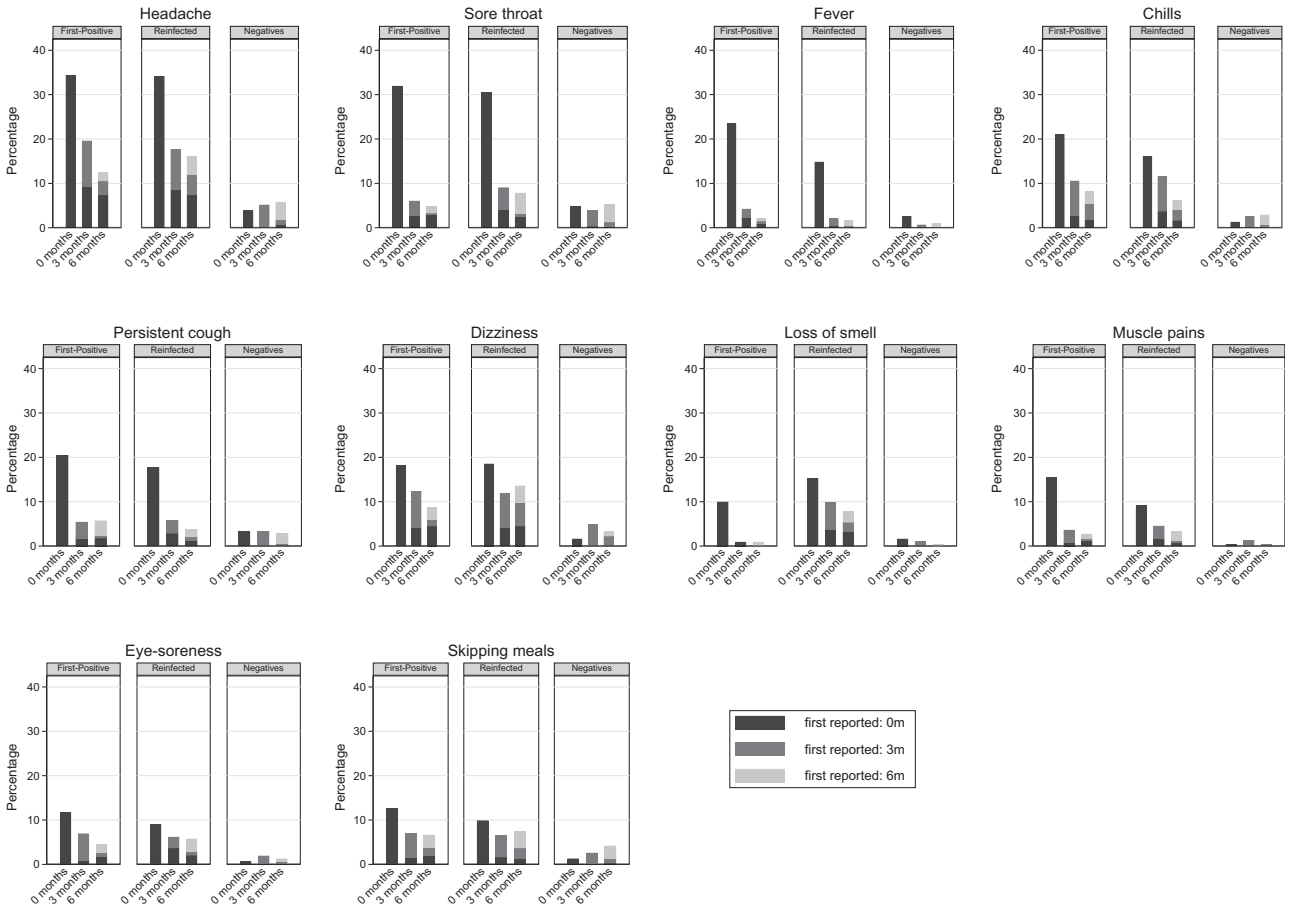

Figure 2. Symptoms where the overall prevalence declined from baseline to 6 months post-test in first positives/reinfected groups.

within-individual prevalence of most reported symptoms decreased over time, the overall prevalence of tiredness, poor sleep, shortness of breath, difficulty concentrating, low mood, and anxiety increased over time with higher prevalences among first positives and reinfected than test negatives (Figure 3). Long COVID at 6 months was numerically more common in those aged 15-17 years compared with their younger counterparts (first positives, 24.3% vs 19.6%; reinfected, 28.1% vs 22.9%; test negatives, 15.1% vs 10.5%), although differences were not statistically significant ($P_{\chi 2} > .22$ for all infection status groups).

Discussion

To our knowledge, this is to investigate long COVID in children and young people first infected or reinfected with SARS-CoV-2 during the period when Omicron was dominant, with follow-up over 6 months and to examine this according to age; 12.1% of children and young people infected for the first time, 16.1% of those reinfected, and 4.8% who always tested negative (by PCR or self-report) met the research definition of long COVID at both 3 and 6 months. It may be the case that the research definition of long COVID is too broad, given that the criterion involves having 1 or more impairing symptom, because less than 4% of children and young sought help from general practitioners, which may be an important behavioral indicator of impairment. Given the scale of infection with Omicron, it is clear that a substantial number of children and young people continue to report experiencing impairing symptoms after infection, albeit few were hospitalized or sought treatment.

We found that, although all groups reported symptoms, the prevalence was always higher in the first positives and reinfected compared with test negatives. There were 2 notable observations. First, symptom profiles were similar to the profiles reported in the original and larger CLoCk study for children and young people infected with earlier variants.[6] Second, for symptoms such as tiredness, poor sleep, and shortness of breath, although within-individual specific symptoms decreased over time, new cohorts experienced these symptoms at 3 and 6 months. Understanding the reason for the emergence of new symptoms months after initial infection is essential. As with previous studies, older children and young people were numerically more likely to

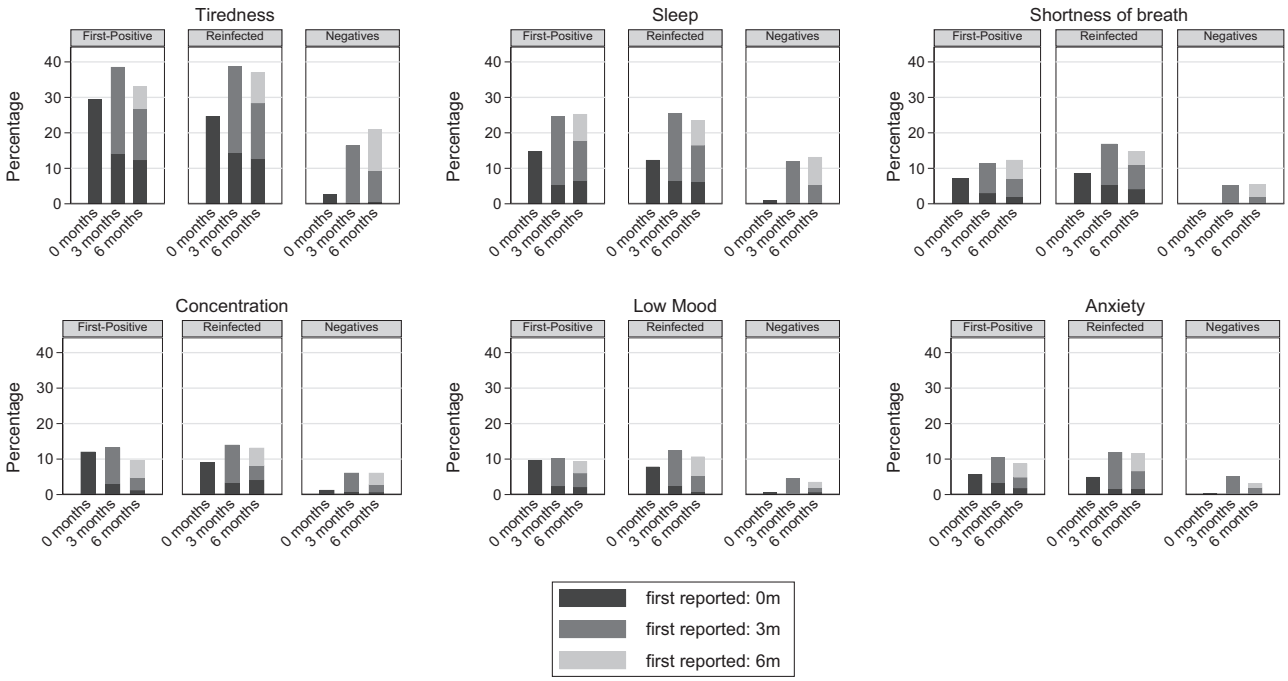

Figure 3. Symptoms where overall prevalence increased or generally stayed high (>10%) over time, in first positives/reinfected groups.

experience long COVID than younger children and young people (although not statistically significant here).[6] Much of the early work in children and young people infected with Omicron focused on very young children; here, we included those aged 11 years and older.[12] Future work would benefit from a lifespan approach including younger children and young people. It should also be considered that successive infection episodes may not be independent of one another in terms of long COVID risk and we might expect some degree of intra-person correlation to exist.

Strengths and limitations of CLoCk study methodology have been described in detail elsewhere.[6] Two limitations of the current report are noteworthy. First, the response rate was 5.9% and it is possible that nonresponse may introduce bias. Moreover, although there were systematic differences between the analytic and target population, the target population (by design, using UK Health Security Agency PCR testing data) might not accurately reflect the general population of children and young people in England or more broadly. Second, we initially set out to determine whether long COVID varied by vaccination status; however, because of data limitations we were unable to appropriately account for vaccine dosage or timing. The latter factor, in particular, may play an important role.[2] Hence, further studies are required to accurately disentangle links between infection and vaccination status and subsequent long COVID. A strength of this study is that symptoms at testing were reported almost immediately and hence recall bias was minimal. Importantly, in this brief report we describe the symptom profiles for 3 infection status groups and do not speculate as to the underlying cause.

Our predominant finding is that children and young people with long COVID after likely infection with Omicron (both first infection and reinfection) have a similar profile to children and young people with long COVID after infection with other variants and that substantial numbers of children and young people are likely to be impacted. ■

Declaration of Competing Interest

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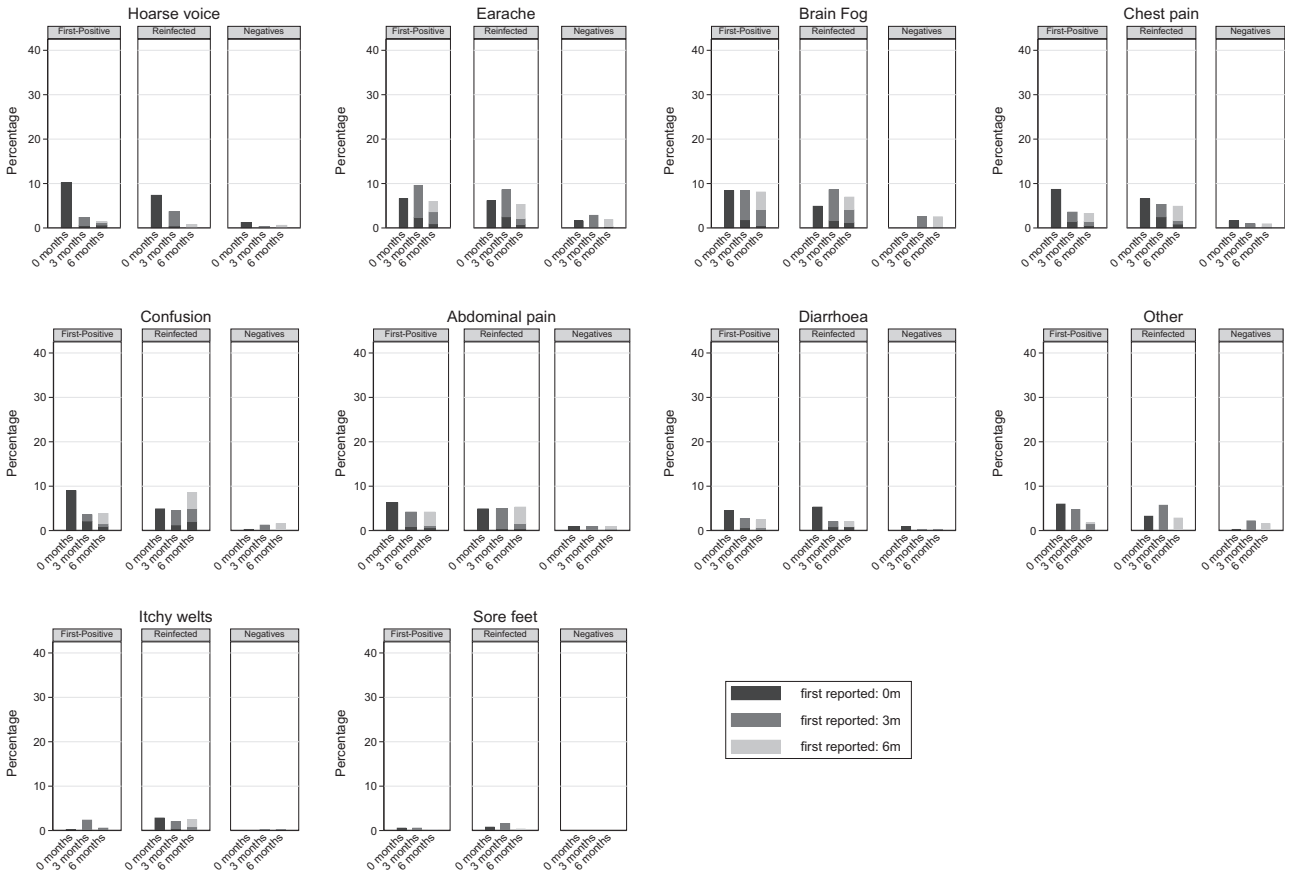

Figure 4. Symptoms with very low overall prevalence (≤10%) at all time points.

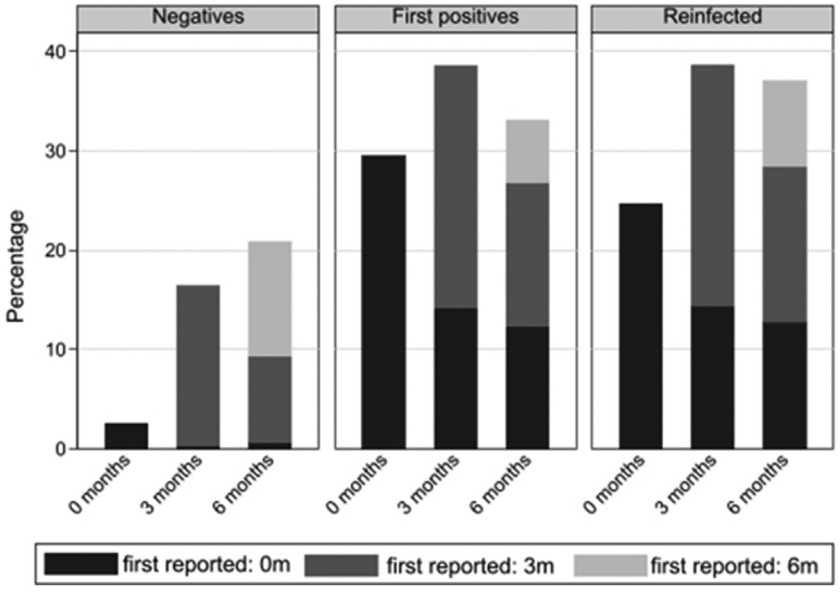

Figure 5. Prevalence of tiredness at time of testing and at 3 and 6 months after testing by infection status.

T.S. is Chair of the Health Research Authority and therefore recused himself from the Research Ethics Application.

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Appendix

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