TITLE: OMICRON-ASSOCIATED CHANGES IN SARS-COV-2 SYMPTOMS IN THE UNITED KINGDOM

TO THE EDITOR:

As the highly-transmissible SARS-CoV-2 Omicron variant increases in incidence, coincident with other winter respiratory viruses circulating in the Northern hemisphere, changes in symptomatology may influence clinical and testing policy. Experimental and clinical data suggest Omicron has less impact on the lower respiratory tract, leading to less severe disease[1], and potentially also affecting other symptoms.

Using the UK Covid-19 Infection Survey, a nationally representative longitudinal household survey[2], we compared symptoms reported in SARS-CoV-2 PCR-positive infection episodes and PCR-negative visits in December-2021, when Omicron emerged and rapidly became dominant UK-wide[3] (**Fig.1A**), with October-2020 to November-2021 (described previously to August-2021[4]). Ethical approval was provided by the South Central Berkshire B Research Ethics Committee (20/SC/0195).

Between October-2020 and December-2021, 53,617 PCR-positive episodes occurred in 52,869 participants (median 40 years, IQR 17-56), with 28,882 (54%) reporting symptoms ("symptomatic PCR-positives"). The comparator comprised 4,236,647 PCR-negative study visits (482,096 participants, median 53 years, IQR 34-67), excluding those with a high pre-test probability of undetected COVID-19 or symptoms from long COVID (see Appendix); 175,479 (4%) self-reported symptoms ("symptomatic PCR-negatives").

As Omicron started to dominate, the percentage of PCR-positives reporting symptoms, and mean number of symptoms reported, declined slightly before rising again (**Fig.1B/C**), potentially due to early Omicron cases being pre-symptomatic when tested, with no change in PCR-negatives. Amongst symptomatic PCR-positives, there was a marked decline in reported loss of taste/smell, from 44%/44% on 1-December-2021 to 13%/11% on 31-December-2021 (**Fig.1D**); loss of taste/smell remained uncommon in symptomatic PCR-negatives throughout (**Fig.1F**). There were concurrent smaller, but significant declines in symptomatic PCR-positives reporting cough, fever, fatigue/weakness, headache, myalgia and shortness of breath with Omicron (**Fig.1D/E**), with little change in symptomatic PCR-negatives (**Fig.1F/G**). Trends were similar for most other symptoms (**Fig.S1**). The key exception was sore throat, increasing from 45% to 59% in symptomatic PCR-positives during December-2021, but also increasing from 41% to 45% in symptomatic PCR-negatives. There was a concurrent trend towards increasing reports of runny nose in symptomatic PCR-positives (**Fig.S1**). Differential symptom reporting between variants, particularly fewer cases with loss of taste/smell and more with sore throat, was unaffected by vaccination status (**Fig.S2**).

Overall, in this study of predominantly mild community-based infection, Omicron was associated with fewer lower and more upper respiratory tract symptoms. Increases in sore throat (also common in symptomatic PCR-negative participants), and the marked reduction in the previously highest specificity symptoms, namely loss of taste/smell, mean Omicron is harder to detect with symptom-based testing algorithms.

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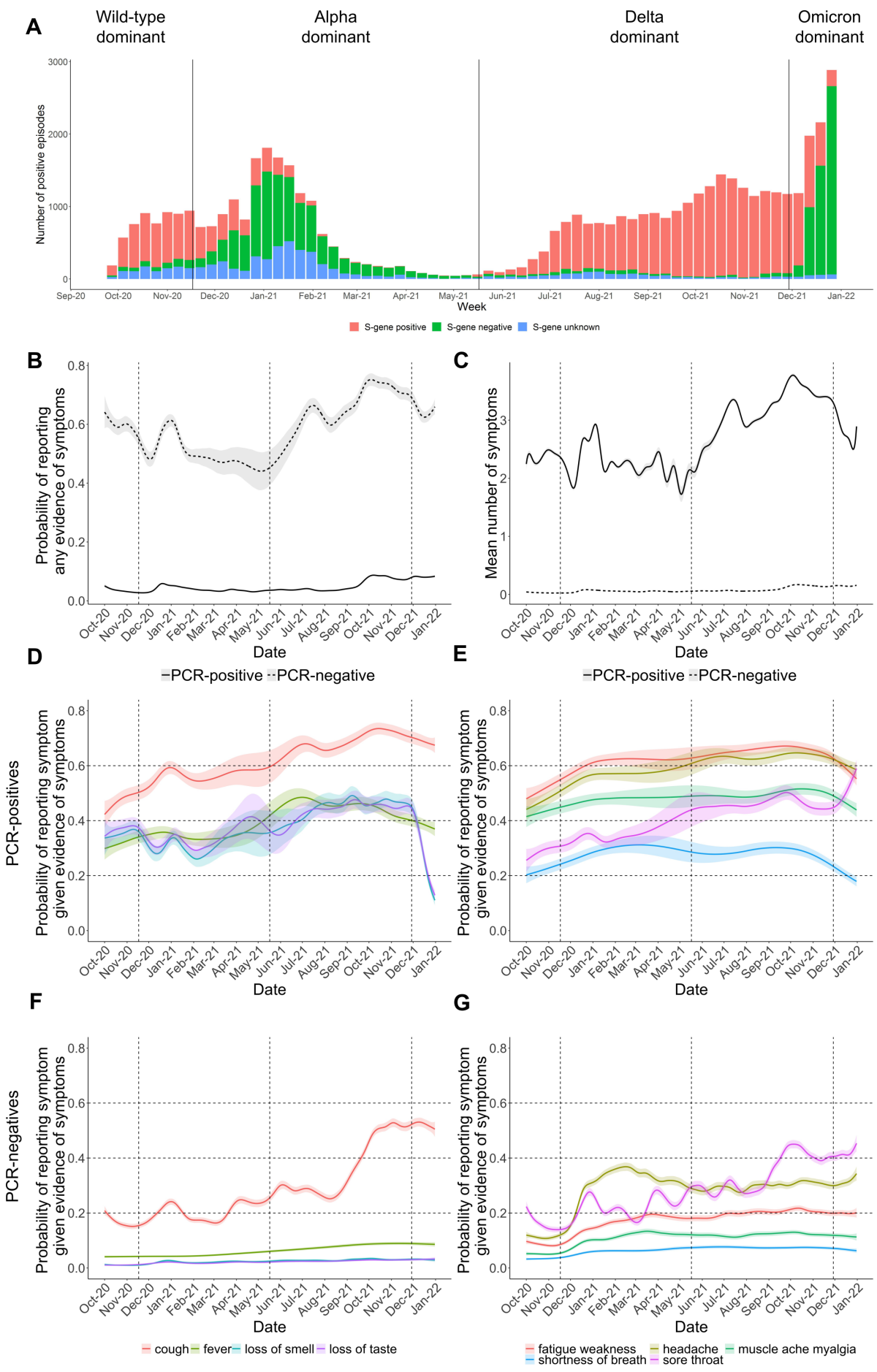
A
Wild-type dominant
Alpha dominant
Delta dominant
Omicron dominant
Number of positive episodes
Week
S-gene positive
S-gene negative
S-gene unknown
B
Probability of reporting any evidence of symptoms
Date
C
Mean number of symptoms
Date
D
PCR-positive
PCR-negative
PCR-positives
Probability of reporting symptom given evidence of symptoms
Date
E
PCR-positive
PCR-negative
Probability of reporting symptom given evidence of symptoms
Date
F
PCR-negatives
Probability of reporting symptom given evidence of symptoms
Date
cough
fever
loss of smell
loss of taste
G
Probability of reporting symptom given evidence of symptoms
Date
fatigue weakness
headache
muscle ache myalgia
shortness of breath
sore throat

Figure 1. Symptoms in those testing positive and negative for SARS-CoV-2 prior to and following the emergence and dominance of Omicron in December 2021 in the UK. Panel A shows the number of PCR-positive infection episodes that were S-gene negative (Alpha-compatible November-2020 to May-2021; Omicron-compatible December-2021) and S-gene positive (Delta-compatible June-2021 onwards). Vertical lines indicate periods when new variants came to dominate: wild type before 17 November 2020, then Alpha before 17 May 2021, then Delta; the first Omicron cases were detected from 29 November 2021. Panels B and C show the probability of reporting symptoms and the number of symptoms (out of the 12 elicited throughout the study period) of all PCR-positive infection episodes and all PCR-negative comparator visits. Panels D-G show the probability of specific symptoms in symptomatic PCR-positive infection episodes (panels D and E) and in symptomatic PCR-negative comparator study visits (panels F and G), after adjustment for age, sex, ethnicity (presented at the reference category age 45, male, white).

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OMICRON-ASSOCIATED CHANGES IN SARS-COV-2 SYMPTOMS IN THE UNITED KINGDOM: SUPPLEMENTARY MATERIAL

Supplementary Methods

This analysis included all SARS-CoV-2 RT-PCR tests of nose and throat swabs from 1-October-2020 to 31-December-2021 in the Office for National Statistics (ONS) Covid Infection Survey (CIS) (ISRCTN21086382, https://www.ndm.ox.ac.uk/covid-19/covid-19-infection-survey/protocol-and-information-sheets). The survey randomly selects private households on a continuous basis from address lists and previous surveys to provide a representative UK sample. Following verbal agreement to participate, a study worker visited each household to take written informed consent, which was obtained from parents/carers for those 2-15 years; those aged 10-15 years provided written assent. Those <2 years were not eligible.

Individuals were asked about demographics, symptoms, contacts and relevant behaviours (https://www.ndm.ox.ac.uk/covid-19/covid-19-infection-survey/case-record-forms). To reduce transmission risks, participants ≥12 years self-collected nose and throat swabs following study worker instructions. Parents/carers took swabs from children <12 years. At the first visit, participants were asked for (optional) consent for follow-up visits every week for the next month, then monthly from enrolment.

Swabs were analysed at the UK's national Lighthouse Laboratories at Milton Keynes and Glasgow using identical methodology. RT-PCR for three SARS-CoV-2 genes (N protein, S protein and ORF1ab) used the Thermo Fisher TaqPath RT-PCR COVID-19 Kit, and were analysed using UgenTec FastFinder 3.300.5, with an assay-specific algorithm and decision mechanism that allows conversion of amplification assay raw data from the ABI 7500 Fast into test results with minimal manual intervention. Samples are called positive if at least a single N-gene and/or ORF1ab are detected (although S-gene cycle threshold (Ct) values are determined, S-gene detection alone is not considered sufficient to call a sample positive).

The presence of 12 specific symptoms in the previous seven days was elicited at each visit from the start of the survey (cough, fever, myalgia, fatigue, sore throat, shortness of breath, headache, nausea, abdominal pain, diarrhoea, loss of taste, loss of smell), as was whether participants thought they had (unspecified) symptoms compatible with COVID-19. Any positive response to any of these symptom questions defined the case as symptomatic. Four additional symptoms (runny nose, trouble sleeping, loss of appetite, wheezing) were added in 29-September-2021; as these were not consistently elicited throughout the survey they are reported separately and not used to define a case as symptomatic.

We included the first positive study test in each PCR-positive infection "episode", defining re-infections (arbitrarily) as occurring ≥120 days after an index positive with a preceding negative test, or after 4

consecutive negative tests[1]. Each positive episode was characterised by viral variant as wild-type/Delta if the S-gene was ever detected (by definition, with N/ORF1ab/both), or as Alpha-compatible or Omicron-compatible if positive at least once for ORF1ab+N, otherwise "other" (N-only/ORF1ab-only) depending on calendar period (**Fig.1A**).

Choice of negative visits in the comparator group

As a comparator group, we initially included all visits where PCR tests were negative, and then, following a previous analysis to August 2021[2], excluded visits where symptoms could plausibly be related to ongoing effects of COVID-19 or long COVID, where there was a high pre-test probability that the participant actually had a new COVID-19 infection that had not been detected in the survey, or where symptoms were likely driven by recent vaccination. Specifically, we excluded all negative visits:

1. **From -90 days before** the first S-antibody positive blood test in the study prior to vaccination, where such antibody results are likely to represent previous undetected infection (these results were available only in a random subset of the population);
2. **From -35 days before** the first swab positive onwards from individuals who ever tested PCR positive in the study or positive on either PCR or LFD in the linked English testing programme (to avoid ongoing long COVID symptoms,[3] and COVID-related symptoms occurring shortly before the positive test);
3. **From -35 days before** any self-reported positive swab test result onwards (for the same reason; reflecting the fact that individuals may have obtained tests elsewhere)
4. From a small number of individuals who reported either loss of taste or loss of smell at their first study visit and had no national testing programme result within [-21,+21] days (all before 1 July 2020), given the high specificity of this symptom for COVID-19 infection, the fact that it would have been impossible for these individuals to get an external test at the time and the potential for subsequent symptoms to represent long COVID;
5. Where participants reported self-isolating OR contact with **definite** positives in the preceding 28 days (since these individuals have much higher risk of SARS-CoV-2 infection which may not have been detected) and the **previous and the next visit** (because of higher risk of unidentified positivity, and because they may have been contact traced through the national training programme they may be more likely to report symptoms through recall bias, regardless of status);

6. Occurring within [-7,+14 days] of either first, second or third vaccination date[4], to avoid the inclusion of common symptoms caused by vaccination in the test-negative comparator group and to reflect the possibility of small inaccuracies in reported date of vaccination for some participants.

Time windows were arbitrary but aligned with other analyses or windows for considering symptoms associated with PCR-positive episodes.

Choice of timeframe to include symptoms in the PCR-positive group

Tests are conducted in the survey independently of symptoms, and therefore infection episodes may be identified either early (pre-symptomatic) or late (post-symptomatic). Symptom questions relate to the previous 7 days, so to ensure that subsequently reported symptoms in pre-symptomatic cases were counted we included all symptoms reported at any visit (PCR-positive/PCR-negative/failed) up to 35 days after the index positive test in each infection episode, reflecting the monthly visit schedule.

Generalised additive models

In regression models for reporting any evidence of symptoms and specific symptoms in those with evidence of symptoms in PCR-positives and PCR-negatives, we truncated age at 85y to avoid undue influence of outliers. Age was modelled as smoothing spline.

```
bam(cbind(n_withsymptom, n_withoutsymptom) ~
s(study_day, bs="bs",  k=50, by=Sars_COV_2_positivity) +
s(age_at_visit, bs="bs",  k=15, by=Sars_COV_2_positivity)  +
sex:Sars_COV_2_positivity + ethnicity_wo:Sars_COV_2_positivity + sex + ethnicity_wo +
Sars_COV_2_positivity, family=binomial(link="cloglog"), method = "fREML", data = data, discrete=TRUE,
nthreads =12)”
```

```
bam(symptom_count ~
s(study_day, bs="bs",  k=50, by=Sars_COV_2_positivity) +
s(age_at_visit, bs="bs",  k=15, by=Sars_COV_2_positivity)  +
```

sex:Sars_COV_2_positivity + ethnicity_wo:Sars_COV_2_positivity + sex + ethnicity_wo + Sars_COV_2_positivity, family=gaussian, method = "fREML", data = data, discrete=TRUE, nthreads =12)

To explore the differences between Delta and Omicron by vaccination status we restricted our PCR-positives to those occurring after 1-December 2021 and classified S-gene positives and S-gene negatives by their vaccination status at the time of the index positive test: before first vaccination (unvaccinated), from 21 days after first vaccination to 13 days inclusive after second vaccination (first vaccine), from 14 days after second vaccination to 13 days inclusive after third vaccination (second vaccine), more than 14 days after the third vaccination (third vaccine).

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Supplementary Figures

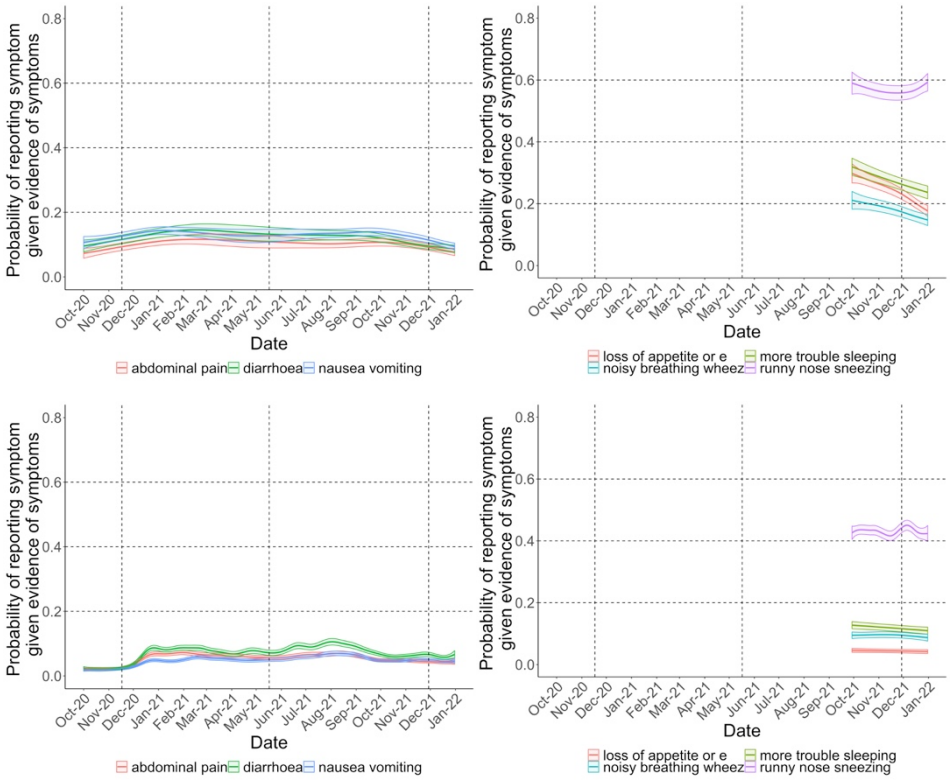

Figure S1. Symptoms in those testing positive and negative for SARS-CoV-2 before following the emergence and dominance of Omicron in December 2021 in the UK. Note: vertical lines indicate periods when new variants came to dominate: wild type before 17 November 2020, then Alpha before 17 May 2021, then Delta; first Omicron cases detected 29 November 2021. Models adjusted for age, sex, ethnicity (presented at the reference category age 45, male, white).

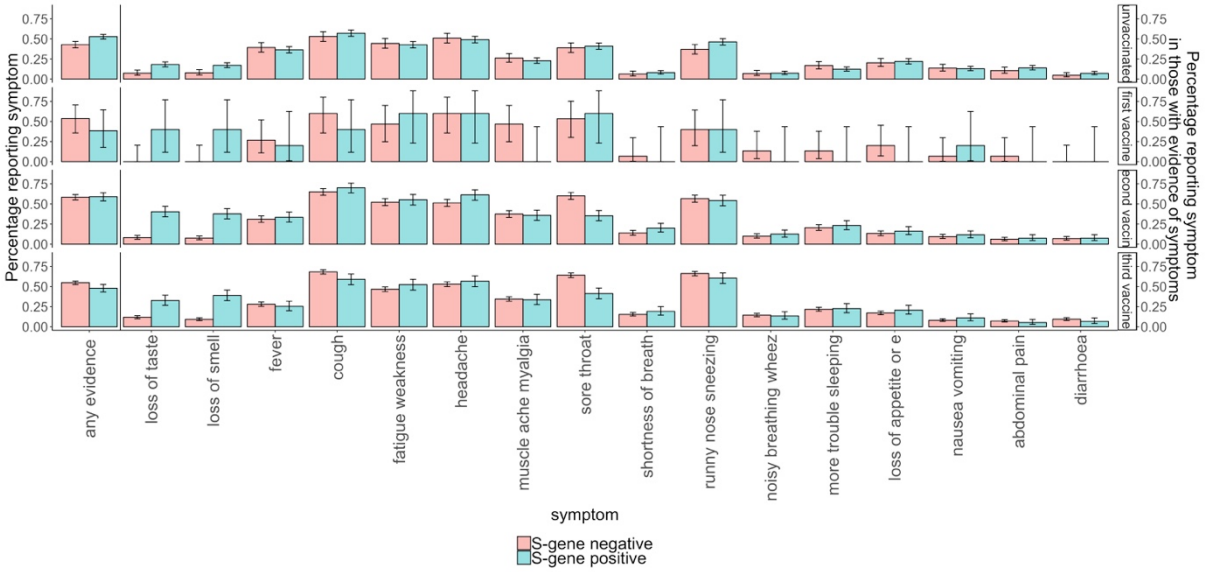

Figure S2. Percentage of S-gene-negative (Omicron-compatible) and S-gene-positive (Delta-compatible) symptomatic PCR-positives in December 2021 reporting different symptoms by vaccination status.

Declarations

Contributors: This specific analysis was designed by ASW, K-DV, KBP, PCM, NS, DWE, TH, DC, TEAP. K-DV conducted the statistical analysis of the survey data. K-DV, NS, PCM, ASW drafted the manuscript. All authors contributed to interpretation of the study results, and revised and approved the manuscript for intellectual content. K-DV is the guarantor and accepts full responsibility for the work and conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author (K-DV) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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PCM received funding from the Wellcome Trust [110110/Z/15/Z]. For the purpose of Open Access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission.

Competing interests: DWE declares lecture fees from Gilead outside the submitted work. No other author has a conflict of interest to declare.

Ethical approval: The study received ethical approval from the South Central Berkshire B Research Ethics Committee (20/SC/0195).

Data sharing: Data are still being collected for the COVID-19 Infection Survey. De-identified study data are available for access by accredited researchers in the ONS Secure Research Service (SRS) for accredited research purposes under part 5, chapter 5 of the Digital Economy Act 2017. For further information about accreditation, contact Research.Support@ons.gov.uk or visit the SRS website.

Transparency: The lead authors affirm that the manuscript is an honest, accurate, and transparent account of the study design being reported, no important aspects of the study have been omitted, and any discrepancies from the study as originally planned (and, if relevant, registered) have been explained. Dissemination to participants and related patient and public communities: Results of individual tests were communicated to the participants. Overall study results were disseminated through the preprint of the study. Findings were disseminated in lay language in the national and local press.

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