Omicron-associated changes in SARS-CoV-2 symptoms in the United Kingdom.

Article Metadata

Authors: Vihta KD, Pouwels KB, Peto TE, Pritchard E, House T, Studley R, Rourke E, Cook D, Diamond I, Crook D, Clifton DA, Matthews PC, Stoesser N, Eyre DW, Walker AS, COVID-19 Infection Survey team

Journal: Clin Infect Dis

Year: 2022

Volume/Issue: 76/3

PMID: 35917440

DOI: 10.1093/cid/ciac613

PubMed URL: https://ncbi.nlm.nih.gov/pubmed/35917440

Full Text (from PubMed Central)

Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America

Oxford University Press

AcademicSubjects/MED00290

Omicron-Associated Changes in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Symptoms in the United Kingdom

https://orcid.org/0000-0002-4111-7577

Nuffield Department of Medicine, University of Oxford

The National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance at the University of Oxford

Department of Engineering, University of Oxford

The National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance at the University of Oxford

Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford

Nuffield Department of Medicine, University of Oxford

The National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance at the University of Oxford

The National Institute for Health Research Oxford Biomedical Research Centre, University of Oxford

Department of Infectious Diseases and Microbiology, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital

Nuffield Department of Medicine, University of Oxford

The National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance at the University of Oxford

Department of Mathematics, University of Manchester

IBM Research, Hartree Centre, Sci-Tech Daresbury

Office for National Statistics

Office for National Statistics

Office for National Statistics

Office for National Statistics

Nuffield Department of Medicine, University of Oxford

The National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance at the University of Oxford

The National Institute for Health Research Oxford Biomedical Research Centre, University of Oxford

Department of Infectious Diseases and Microbiology, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital

Department of Engineering, University of Oxford

Nuffield Department of Medicine, University of Oxford

Francis Crick Institute

Division of Infection and Immunity, University College London

Department of Infection, University College London Hospitals

https://orcid.org/0000-0002-4508-7969

Nuffield Department of Medicine, University of Oxford

The National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance at the University of Oxford

The National Institute for Health Research Oxford Biomedical Research Centre, University of Oxford

Department of Infectious Diseases and Microbiology, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital

The National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance at the University of Oxford

The National Institute for Health Research Oxford Biomedical Research Centre, University of Oxford

Big Data Institute, Nuffield Department of Population Health, University of Oxford

Nuffield Department of Medicine, University of Oxford

The National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance at the University of Oxford

The National Institute for Health Research Oxford Biomedical Research Centre, University of Oxford

COVID-19 Infection Survey team

D. W. E. and A. S. W. contributed equally to this work.

Correspondence: Karina-Doris Vihta, Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, Oxford OX1 2JD, United Kingdom (

karina-doris.vihta@eng.ox.ac.uk

Potential conflicts of interest.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Delta variant has been replaced by the highly transmissible Omicron BA.1 variant, and subsequently by Omicron BA.2. It is important to understand how these changes in dominant variants affect reported symptoms, while also accounting for symptoms arising from other cocirculating respiratory viruses.

In a nationally representative UK community study, the COVID-19 Infection Survey, we investigated symptoms in polymerase chain reaction (PCR)–positive infection episodes versus PCR-negative study visits over calendar time, by age and vaccination status, comparing periods when the Delta, Omicron BA.1, and BA.2 variants were dominant.

Between October 2020 and April 2022, a total of 120 995 SARS-CoV-2 PCR-positive episodes occurred in 115 886 participants, with 70 683 (58%) reporting symptoms. The comparator comprised 4 766 366 PCR-negative study visits (483 894 participants), with symptoms reported at 203 422 visits (4%). Symptom reporting in PCR-positive infections varied over time, with a marked reduction in loss of taste/smell as Omicron BA.1 dominated, which was maintained with BA.2 (44% symptomatic infections reporting loss of taste/45% symptomatic infections reporting loss of smell on 17 October 2021, 16%/13% 2 January 2022, 15%/12% 27 March 2022). Cough, fever, shortness of breath, myalgia, fatigue/weakness, and headache also decreased after Omicron BA.1 dominated, but sore throat increased, the latter to a greater degree than concurrent increases in PCR-negative visits. Fatigue/weakness increased again after BA.2 dominated, although to a similar degree to concurrent increases in PCR-negative visits. Symptoms were consistently more common in adults aged 18–65 years than in children or older adults.

Increases in sore throat (also common in the general community), along with a marked reduction in loss of taste/smell, make Omicron harder to detect with symptom-based testing algorithms, with implications for institutional and national testing policies.

In a UK community study, loss of taste/smell was markedly less commonly reported with Omicron BA.1/BA.2 than with Delta severe acute respiratory syndrome coronavirus 2 infections, with smaller declines in reported shortness of breath, myalgia, and fatigue/weakness but increases in sore throat, challenging symptom-based testing algorithms.

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10.13039/501100010753

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Highly-transmissible severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variants, BA.1 and BA.2, emerged and become dominant at the end and start of 2021 and 2022, 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 that Omicron has less impact on the lower respiratory tract, leading to less severe disease [

We used the UK COVID-19 Infection Survey, a nationally representative longitudinal household study [

This analysis was based on SARS-CoV-2 PCR tests of nose and throat swab samples taken regularly between 1 October 2020 and 23 April 2022 from participants in the Office for National Statistics COVID-19 Infection Survey (ISRCTN21086382;

https://www.ndm.ox.ac.uk/COVID-19/COVID-19-infection-survey/protocol-and-information-sheets

Individuals were asked about demographics, symptoms, contacts and relevant behaviors (

https://www.ndm.ox.ac.uk/COVID-19/COVID-19-infection-survey/case-record-forms

Supplementary Table 1

Swab samples were analyzed at national Lighthouse Laboratories at Milton Keynes and Glasgow, using identical methods. PCR for 3 SARS-CoV-2 genes (N protein, S protein and open reading frame (ORF)1ab) was performed using the Thermo Fisher TaqPath RT-PCR coronavirus disease 2019 (COVID-19) kit, and analyzed using UgenTec FastFinder 3.300.5, with an assay-specific algorithm and decision mechanism that allows conversion of amplification assay raw data into test results with minimal manual intervention. Samples are called positive if at least the N-gene and/or ORF1ab are detected. Although S-gene cycle threshold values are determined, S-gene detection alone is not considered sufficient to call a sample positive, according to the assay manufacturer [

The presence of 12 specific symptoms in the previous 7 days was elicited at each visit from the start of the survey (cough, fever, myalgia, fatigue/weakness, sore throat, shortness of breath, headache, nausea, abdominal pain, diarrhea, loss of taste, loss of smell), as was whether participants thought they had (unspecified) symptoms compatible with COVID-19. Positive response to any of these questions defined “symptomatic” cases. Four additional symptoms (runny nose, trouble sleeping, loss of appetite, wheezing) were added from 29 September 2021; because these were not elicited throughout the survey, they were considered separately and not used to define symptomatic cases.

We grouped repeated PCR-positive test results into infection “episodes” [

Supplementary Methods

As a comparator, we initially considered all visits with negative PCR test results, and then, after a previous analysis to August 2021 [

Supplementary Methods

Generalized additive models (binomial distribution with complementary log-log link) were fitted to estimate the percentage of PCR-positive infection episodes and PCR-negative visits for which participants were symptomatic, and the percentage of each of these for each symptom separately. Models adjusted simultaneously for calendar time (smoothing spline), age (smoothing spline), sex, and ethnicity (white vs nonwhite). From 29 September 2021 onward, fitted models with an additional interaction between age and time were used to present differences in symptoms by age.

To explore differences between Delta, Omicron BA.1, and Omicron BA.2 infections by vaccination status and infection/reinfection, we restricted PCR-positive infection episodes to those occurring after 29 September 2021 and classified S-gene–negative infections occurring after 1 December 2021 as Omicron BA.1 compatible (34 576 infections; 20 345 [59%] symptomatic), and S-gene–positive infections from 29 September 2021 to 2 January 2022 as Delta compatible (14 318 infections; 9030 [63%] symptomatic) and from 30 January to 23 April 2022 as Omicron BA.2 compatible (34 796 infections; 2 591 [65%] symptomatic) (excluding S-gene–positive infections from 3 to 29 January 2022 because both Delta and Omicron BA.2 infections occurred during this period and genetic sequences were not available for all PCR-positive results). Descriptive analyses are presented of differences in symptom presence or absence and specific symptoms by variant, vaccination status, and infection episode. Comparisons by vaccine status are restricted to participants ≥18 years old to reduce confounding arising from lower vaccination rates in those <18 years old.

All analyses were performed using R 3.6.1 software. Generalized additive models were fitted using mgcv 1.8–31; example code is provided in the

Supplementary Methods

Between October 2020 and April 2022, a total of 120 995 PCR-positive episodes occurred in 115 886 participants (median age, 44 years; IQR, 24–61 years), 70 683 (58%) with reported symptoms; 8898 of 120 995 (7%) were reinfections (

Supplementary Figure 1

While Omicron BA.1 infections dominated (19 December 2021 to 26 February 2022, when >50% of PCR-positive results were S-gene negative), the percentage of PCR-positive infection episodes with reported symptoms was lower compared with much of the previous time period when the Delta variant dominated (6 June to 18 December 2021;

For specific symptoms, among symptomatic PCR-positive infection episodes, there was a marked decline in reported loss of taste/smell for both Omicron variants, BA.1 and BA.2, from high levels during the period when Delta dominated, from 44% reporting loss of taste/45% reporting loss of smell on 17 October 2021 (approximately peak Delta;

There were concurrent smaller, but significant, declines in symptomatic PCR-positive infection episodes with reported cough, fever, fatigue/weakness, myalgia, shortness of breath, or headache during December 2021, as Omicron BA.1 dominated (

In contrast to these declines in other symptoms as Omicron BA.1 dominated, sore throat became more commonly reported with BA.1 and increased further with BA.2, from 46% to 56% in symptomatic PCR-positive infection episodes during December 2021, increasing to 64% by April 2022. Similarly to cough, sore throat became more commonly reported at PCR-negative visits during October 2021, if anything dropping slightly in January 2022, from 43% to 33%, before increasing again to 42% by 23 April 2022 (

Gastrointestinal symptoms were reported infrequently in symptomatic PCR-positive infection episodes regardless of variant and were reported at similar frequencies at PCR-negative visits (

Supplementary Figure 2

Supplementary Figure 2

In participants aged ≥18 years, differences in symptoms between Delta and Omicron infections, including fewer cases with loss of taste/smell and more with sore throat, were broadly similar across all vaccination statuses (

Supplementary Figure 3

Supplementary Table 2

Supplementary Figure 4

Percentage of polymerase chain reaction (PCR)–positive infection episodes reporting symptoms by variant and by vaccination status (restricting to those aged ≥18 years), showing reporting of any evidence of symptoms as well as specific symptoms in symptomatic PCR-positive infection episodes from 29 September 2021 onward (not adjusted for other factors; see

Supplementary Table 2

Percentage of polymerase chain reaction (PCR)–positive infection episodes reporting symptoms by variant and infection/reinfection, based on reporting of any evidence of symptoms, as well as specific symptoms in symptomatic PCR-positive infection episodes from 29 September 2021 onward (not adjusted for other factors; see

There were differences in reported symptoms with these different variants by age when comparing reported symptoms at the peaks of the Delta, BA.1 and BA.2 waves (

Supplementary Figure 5

Supplementary Figure 6

By age, estimated percentage of polymerase chain reaction (PCR)–positive infection episodes and comparator PCR-negative study visits reporting symptoms and mean number of symptoms at the peaks of Delta, Omicron BA.1, and Omicron BA.2 waves. Model estimates are shown for reporting of any evidence of symptoms as well as specific symptoms in symptomatic PCR-positive infection episodes and comparator PCR-negative study visits on 17 October 2021 (Delta), 2 January 2022 (when Omicron BA.1-compatible infections represented the highest proportion of PCR-positive infections), and 27 March 2022 (when Omicron BA.2 was the dominant variant). Panels in the first row show the probability of reporting symptoms and the number of symptoms (of the 12 elicited throughout the study period) in all PCR-positive infection episodes and all PCR-negative comparator visits from 29 September 2021 onward, estimated at 3 reference categories, 17 October 2021, 2 January 2022, and 27 March 2022. The remaining panels show the probability of reporting specific symptoms in symptomatic PCR-positive infection episodes and in symptomatic PCR-negative comparator study visits at these reference categories. All are adjusted for calendar date, age (allowing for effect modification by calendar date by including an interaction between calendar date and age), sex (reference category: male), and ethnicity (reference category: white). See

Supplementary Figure 3

Loss of taste or smell was most commonly reported with Delta infections in adults aged 18–70 years but was reported at lower levels in older adults and rarely in younger children; with Omicron BA.1/BA.2 infections, it was seen only at low levels, regardless of age. Variations in the percentage of symptomatic participants reporting most other specific symptoms across ages were broadly similar before versus after dominance of Omicron BA.1, but slightly higher percentages of participants >70 years of age with symptomatic PCR-positive infection episodes reported fever, headache, fatigue/weakness, or muscle ache/myalgia after Omicron BA.1/BA.2 dominated (

Supplementary Figure 6

The net result of changes in the symptom profile, overall and by age, was that fever and cough became most strongly associated with PCR positivity in those reporting symptoms after Omicron BA.2 became dominant, adjusting for age, sex, and ethnicity (see

Supplementary Methods

Supplementary Figure 7

In this study of predominantly mild community-based infection, Omicron BA.1 and BA.2, compared with Delta, were associated with less loss of taste, loss of smell, shortness of breath, myalgia, fatigue/weakness, and headache but more sore throat. The overall probability of reporting any symptoms was similar for Delta and BA.2 but lower for BA.1 regardless of age, while the mean number of symptoms reported was generally lower for both BA.1 and BA.2 compared with Delta across ages, although higher overall for BA.2 than BA.1. However, this was driven by symptoms in adults; in the youngest and oldest participants, there was no evidence of difference between BA.2 and Delta in the percentage reporting any symptoms, and a higher mean number of symptoms was reported with BA.2 in the very youngest and oldest participants, compared to both BA.1 and Delta.

In PCR/lateral flow antigen–positive cases, the ZOE study, which relies on volunteers reporting symptoms daily using an app, found a lower median number of symptoms reported in infections from 28 November 2021 to 17 January 2022 (predominantly Omicron BA.1) than from 1 June to 27 November 2021 (predominantly Delta), with matching by age, sex, and ethnicity in volunteers who had had a second or third vaccine [

This provides a representative sample of PCR-negative visits without SARS-CoV-2 infection for comparison with symptom rates for PCR-positive infection episodes. This is important because some symptoms reported in PCR-positive infections could be due to coinfections with other circulating respiratory viruses. Therefore, although our study does not specifically test for other viruses, we can estimate whether changes seen with Omicron BA.1 and BA.2 differ from underlying trends in the general population (

Intriguingly, we found that the differences between variants in the probability of reporting specific symptoms in symptomatic PCR-positive infection episodes persisted regardless of vaccination status or whether the infection was the first or a subsequent infection, while the probability of reporting symptoms was smaller for reinfections than for first infections. A limitation is that this analysis is of unadjusted percentages, and therefore the lack of observed differences by vaccination status within a variant could be at least partly due to confounding with age, as well as other factors, such as previous infection, which could lead to choosing not to be vaccinated or to get only a single vaccine (only 3% of the infections included in this analysis). However, most symptoms were reported similarly in adults aged 18 to about 60–70 years (

Other limitations of the current study include the fact that we cannot have certainty in determining reinfections given the data available; however, estimated reinfections were infrequent (7%), even once Omicron dominated (11%),

Citation

Vihta KD, Pouwels KB, Peto TE, Pritchard E, House T, Studley R, Rourke E, Cook D, Diamond I, Crook D, Clifton DA, Matthews PC, Stoesser N, Eyre DW, Walker AS, COVID-19 Infection Survey team. Omicron-associated changes in SARS-CoV-2 symptoms in the United Kingdom.. Clin Infect Dis. 2022. DOI: 10.1093/cid/ciac613