A comparison of symptom prevalence, severity and duration in the SARS-CoV-2 Omicron vs Delta variants among vaccinated individuals from the ZOE COVID Study

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Abstract

Background: The most recent dominant SARS-CoV-2 variant of concern, Omicron, maybe less severe than the previously dominant variant, Delta. The aim of this study is to quantify the differences in their symptoms, severity, and duration among the vaccinated (two or three doses) population in the UK.

Methods: 62,002 UK participants from the ZOE COVID App testing positive for SARS-CoV-2 and reporting symptoms were matched 1:1 on age, sex, and vaccination dose across two periods: from June 1st, 2021, to November 27th, 2021, (Delta dominant, N=4,990) and from December 22nd, 2021, to January 17th, 2022 (Omicron dominant, N=4,990). We compared the prevalence of the 32 COVID-19 related symptoms, their duration, and the severity of the acute infection.

Results: The symptoms of infection with Omicron were significantly different from those by the Delta variant. For Omicron, loss of smell was less prevalent (16.7% versus 52.7%, OR = 0.17 [95%CI: 0.16 - 0.19], p<0.001) and sore throat was more frequent (70.5% versus 60.8%, OR = 1.55 [95%CI: 1.43 -1.69], p<0.001). The duration of symptoms was significantly shorter (6.87 [95%CI: 6.58 - 7.16] days, versus 8.89 [95%CI: 8.61 - 9.17] days) and there was a lower rate of hospitalisation (1.9% versus 2.6%, OR = 0.75 [0.57 - 0.98], p = 0.03).

Interpretation: The prevalence of symptoms that characterise an Omicron infection differ from those of the Delta SARS-CoV-2 variant, with apparently less involvement of the lower respiratory tract, need for hospitalisation, and a shorter duration of the acute phase in vaccinated people.

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Key words: COVID-19; variants of concern; Omicron; Delta; vaccination, SARS-CoV-2

Research into context

Evidence before the study

We searched PubMed for articles published up to January 24th, 2022, using the terms “SARS-CoV-2 Omicron symptoms” and “SARS-CoV-2 Omicron hospitalisation”. We found several published papers and preprints covering differences in viral load, neutralising antibody responses among vaccinated individuals and the description of prevalence in various regions (Florida, Norway, South Africa).

A recent large data linkage study from South Africa indicated that the Omicron variant was significantly less severe than with the previous dominant variants, with lower rates of hospital admission.

A recent small study from Korea (n=40) has shown that symptoms for Omicron were mild with none of the cases needing supplemental oxygen.

However, the general presentation of symptoms compared to Delta and how the duration and severity vary between two or three doses of the vaccine has not been reported on a large prospective population scale.

Added value of this study

This is a larger, more detailed, generalizable, and less confounded study than attempted previously. We report that the symptoms characterising an Omicron break-through infection differ from those of the Delta SARS-CoV-2 variant, with significantly less involvement of the respiratory tract, very rare loss of a sense of smell or taste, more sore throat, a shorter duration of the acute illness, and lower hospitalisation rates. Since we matched on age, sex and number of vaccine doses, these factors are unlikely to confound our observation.

Implications of all the available evidence

In this vaccinated population, the Omicron SARS-CoV-2 variant has a different clinical presentation to that of previous waves of COVID-19, with a lower rate of hospitalisation, number of symptoms, and shorter duration of acute symptoms. The different clinical presentation is important for selection of testing-triggering symptoms

Introduction

On November 26th, 2021, the World Health Organisation designated the variant B.1.1.529, named Omicron, first seen in South Africa, a new variant of concern [1]. Omicron presents several mutations, >30 of which in the spike protein and 15 within the receptor-binding domain, which may impact its transmission, disease presentation and natural or vaccine-induced protective immunity [1]. Over the past several weeks, Omicron has spread in over 80 countries and has become the dominant SARS-CoV-2 variant in the UK due to its rapid spread overtaking the previously dominant Delta variant (B.1.617.2) on December 22nd, 2021 [2]. Early reports suggest infection with Omicron is less severe than with previous variants[3–5] . A South Korean report[4] described the clinical presentation of Omicron cases; there were no severe cases in the limited sample size (n = 40). Hospital admission rates in South Africa for cases infected with this variant have been significantly lower than for previous waves (where other variants of concern were dominant)[5,6].

However, as of today no detailed report on symptom prevalence, severity, and acute symptom duration, and how these compare to the Delta variant, have been published.

The aim of this study is to quantify the differences in symptoms, severity (measured as hospitalisation), and duration following infection with either Omicron or Delta variants among the vaccinated (two or three doses) population in a large community cohort from the UK drawn from the ZOE COVID Study app.

Methods

A CONSORT diagram, presented in **Supplementary Figure 1**, illustrates the study design, and the analytical pipeline to generate the study samples.

Study Setting and Participants

We collected prospective longitudinal observational data using the ZOE COVID Study, previously known as the COVID Symptoms Study App[7]. The app enables self-reported information related to SARS-CoV-2 infection to be captured. Briefly, upon enrolment users provided baseline

demographic and health information. Subsequently, participants provided daily updates on symptoms experienced, SARS-CoV-2 test results, vaccines administered, and if they were self-quarantining or seeking health care, including the level of intervention and related outcomes. Users can also proxy-report for others. Ethical approval for use of the app for research purposes in the UK was obtained from King's College London Ethics Committee (review reference LRS-19/20-18210), and all users provided consent for non-commercial use.

Procedures

We included data from all UK participants aged 16 to 99 years (including proxy-reported individuals), with a BMI between 15 and 55, who had at least two doses of any Sars-CoV-2 vaccine, were symptomatic and logged a positive symptomatic Polymerase Chain Reaction (PCR) or lateral flow antigen test (LFAT) for SARS-CoV-2 between June 1st, 2021, and January 17th, 2022 (cut-off date). The full list of symptoms queried is presented in the **Table S1**.

Outcomes

Our primary outcome were the odds of developing a given symptom (out of the 32 asked about in the app) within 7 days before or after the positive test (e.g., self-reported LFAT or PCR test positivity) in those likely infected with Omicron compared to those infected in the Delta-predominant period. We also calculated the odds of (i) reporting any of the classic symptoms (i.e., fever, loss of smell and persistent cough[7]) and of (ii) having severe COVID-19 (measured as reported visit to hospitalisation within the disease period) in those infected with Omicron compared to Delta.

Our secondary outcome was symptoms duration for Omicron versus Delta. Acute symptom duration was calculated as the difference between the "onset date" (date of reported symptoms) and "recovery date" (the first day where users reported feeling normal, which was not followed by a day with reported symptoms for at least one week). For this secondary analysis, we included a subset of individuals who reported at least weekly, from first symptom report until returning to symptom-freedom and had recovered within 21 days, given the recent onset of Omicron, to allow us to include a sufficient numbers of individuals.

Statistical Analysis

We compared data from two time periods: June 1st, 2021, to November 27th, 2021, when the Delta variant was dominant (prevalence >70%); and December 22nd, 2021, to January 17th, 2022, when Omicron became dominant in the UK (prevalence >70%). Through a Euclidean distance-based algorithm [8], individuals with Omicron infection were matched 1:1 to individuals with Delta infection on age, sex, and vaccination doses. We were unable to match for SARS-CoV-2 prevalence, tiered lockdown restrictions, or vaccination rates, which varied widely across the community and over time during this study.

Baseline characteristics are presented as the number (percentage) for categorical variables and the mean (standard deviation) for continuous variables.

Multivariable logistic regressions were employed to investigate the odds of developing symptoms and of having a severe outcome in those infected with Omicron compared to those infected with Delta, adjusting for age, sex, presence of comorbidities and vaccination status (2 versus 3 doses) and multiple testing (using Benjamini Hochberg correction). We assessed risk of developing specific symptoms within 7 days from/to the positive test. Multivariable logistic regression adjusting for covariates was also employed to investigate whether symptom duration significantly differed among those infected with Omicron versus Delta. For this analysis, we compared the odds of symptoms lasting for over 7 days with the odds of symptoms lasting less than 7 days.

We also conducted sensitivity analyses stratifying according to number of vaccine doses to minimise the influence of confounding by vaccination status in the clinical presentation of the two variants. We were not able to run comparable matched analyses in the unvaccinated and in those with only one dose due to the low number of unvaccinated or individuals vaccinated with a single dose.

Results

We included 63,002 app users who (i) tested positive for SARS-CoV-2 (self-reported PCR/LFAT) (ii) reported symptoms within the requisite timeframes; and (iii) logged at least weekly, from first symptom report until returning to symptom-freedom for calculation of illness duration. Out of these,

33,785 users tested positive when Delta was dominant, while 29,217 when Omicron was dominant. After 1:1 matching, the total number of participants in each of the two groups reduced to 4,990. The demographic characteristics of the study population are presented in **Table 1**.

Symptoms Prevalence

Among those reporting one or more potential symptoms of COVID-19, in the matched group and testing positive when Delta was dominant, the most frequently reported symptoms were runny nose (4,073 out of 4,990 individuals, 81.6%), headache (3,888 out of 4,990 individuals, 77.9%), sneezing (3,529 out of 4,990 individuals, 70.7%), sore throat (3,033 out of 4990 individuals, 60.8%) and loss of smell (2,631 out of 4,990 individuals, 52.7%). Among those testing positive when Omicron was dominant, the most frequently reported symptoms were runny nose (3,818 out of 4,990 individuals 76.5%), headache (3,729 out of 4,990 individuals, 74.7%), sore throat (3517 out of 4990 individuals, 70.5%), sneezing (3,143 out of 4,990 individuals, 63.0%) persistent cough (2,486 out of 4,990 individuals, 49.8%) and hoarse voice (2,145 out of 4,990 individuals, 42.6%) (**Figure 1A**). The breakdown of symptoms prevalence in the 7 days before and after the positive test is depicted in **Figure 1A**. Symptom prevalence in this 1:1 matched subset was consistent with overall prevalence in the larger set of 62,002 cases (**Supplementary Figure 2**).

We then assessed the difference in the prevalence of the various symptoms by deriving an odds ratio for Omicron vs Delta (i.e., the odds of a symptom being prevalent among Omicron infected individuals compared to Delta infected individuals) (**Figure 1B**). We found that out of the 32 symptoms assessed, 12 were significantly less prevalent among Omicron infected individuals than among those infected during the Delta dominant period. Moreover, a sore throat and hoarse voice were significantly more likely to be present among Omicron infections than Delta infections (sore throat: OR = 1.55 [95%CI: 1.43 - 1.69], p < 0.001; hoarse voice: 1.237 [1.14 - 1.34], p < 0.001): conversely, loss of smell (OR = 0.17 [95%CI: 0.16 - 0.19], p < 0.001), altered sense of smell (OR = 0.54 [95%CI: 0.50 - 0.59], p < 0.001), sneezing (OR = 0.70 [95%CI: 0.65 - 0.76], p < 0.001), runny nose (OR = 0.73 [95%CI: 0.67 - 0.81], p<0.001), brain fog (OR = 0.78 [95%CI: 0.71 - 0.85], p<0.001), eye soreness (OR = 0.81 [95%CI: 0.74 - 0.88], p < 0.001), headache (OR = 0.84 [95%CI: 0.77, 0.93], p<0.001), and fever (OR = 0.87 [95%CI: 0.80 - 0.94], p < 0.001) were all significantly less prevalent among Omicron compared with Delta cases.

Furthermore, we report that individuals infected during the Omicron dominant period were less likely to display at least one out of the three “classic” COVID-19 symptoms (fever, loss of smell,

persistent cough) compared to individuals infected with Delta (OR = 0.56 [95%CI: 0.51 - 0.61], p<0.001 (**Figure 2A**)).

Finally, we also conducted a sub-analysis assessing the odds ratios by vaccination status (**Supplementary Table 1, Figure 2A**), which showed consistent results.

Severity

We found that among double vaccinated and boostered individuals combined, there was lower risk of hospitalisation following an Omicron infection (Omicron: 94 out of 4,990 individuals, 1.9%; Delta: 130 out of 4,990, 2.6%, OR = 0.75 [95%CI: 0.57 - 0.98], p < 0.05) **Figure 2B**. Given the relatively small number of hospitalised patients in this community-based study, this effect did not reach statistical significance in the separate 2-dose and 3-dose groups, but in both, the effects were similar (**Figure 2B**).

Symptom Duration

In a subset of individuals that recovered within 21 days, we compared the number of days spanned until resolution of acute symptoms in which matched Delta-infected and Omicron-infected individuals (1,530 each). We found that the duration of acute symptoms was slightly longer for Delta (mean symptom duration = 8.89 [95%CI: 8.61 - 9.17] days, median 8.0, IQR 5.0 - 12 days]) compared to Omicron (mean symptom duration = 6.87 [95%CI: 6.58 - 7.16] days, median= 5.0; IQR 3.0 - 9.0 days, p < 0.001) (**Figure 2C)**. This difference appeared less marked among individuals who had received only two doses of the vaccine (**Figure 2D)** (Delta mean duration = 9.57 [95%CI: 9.22 - 9.92] days, median 9.0; IQR 6 - 13 days; Omicron mean symptom duration= 8.30 [95%CI: 7.96 - 8.65] days, median 7.0, IQR 4 - 11 days, p < 0.001) and more marked in those who had received three doses of the vaccine (**Figure 2E)** (Delta mean duration = 7.71 [95%CI: 7.26 - 8.15] days, median 7.0, IQR 4 - 10 days; Omicron mean symptom duration = 4.40 [3.98 - 4.82] days, median 3.0, IQR 2 - 5 days, p < 0.001). Finally, we assessed, in this same subset of individuals the odds among Omicron-dominant infections of recovering within 7 days of the onset of symptoms compared to infections during the Delta-dominant period. We

obtained an odds ratio (adjusted for age, sex, presence of comorbidities and vaccine doses) of OR = 2.49 [95% CI: 2.10 - 2.95] indicating that Omicron infections are twice as likely to recover within one week of the onset of symptoms than Delta infections.

Discussion

The symptoms that characterise an Omicron infection differ moderately from those of previous SARS-CoV-2 variants. The two symptoms that were consistently more prevalent among Omicron than among Delta cases (regardless of vaccination status) were sore throat and hoarse voice. On the other hand, seven out of the 32 symptoms assessed were significantly less prevalent among Omicron than among Delta cases, in both vaccination groups, and 12 out of the 32 symptoms were significantly less prevalent overall. The most striking difference was observed for loss of sense of smell, a pathognomonic feature of earlier waves of SARS-CoV-2 infection[7], yet now present in under 20% of cases. Moreover, many debilitating symptoms, like brain fog, eye burning, dizziness, fever, and headaches were all significantly less prevalent in Omicron cases.

In addition, hospital admission was significantly lower among Omicron than Delta cases. This supports previous findings from South Africa and Korea that showed the Omicron variant to be milder in terms of severity [4, 5, 6]. Finally, we observed that the duration of acute symptoms was shorter with the average presentation of Omicron being 2-days shorter than that of Delta. Furthermore, a third dose gave a greater reduction in symptom duration in those infected during the Omicron period, than the Delta period.

SARS-CoV-2 is known to affect diverse organ sites including, in addition to the respiratory tract, dermatological complications, myocardial dysfunction, gastrointestinal symptoms, neurologic illnesses, hepatic and renal injury [9, 10]. Multiple organ involvement is particularly noticeable in severe cases [11]. Our data indicating a narrower spectrum and shorter resolution of symptoms along with a milder presentation than the previous dominant variant (Delta) all concur with the current view that although Omicron appears to be much more transmissible than previous variants [12] it is less severe in the vaccinated populations [13]. Our finding that the odds of hospitalisation are 25% lower for Omicron than for Delta are consistent with reports by the South African private health insurer Discovery Health in Johannesburg, which announced that hospitalisation risk has been 29% lower among people infected with Omicron[13].

The sequence of SARS-CoV-2 Omicron virus has some deletions and more than 30 mutations compared to the original sequence [14]. Several of the mutations overlap with those present in the previous variants of concern and are known to increase transmissibility; other Omicron mutations with known effects confer an increase in transmissibility and affect binding affinity [15]. But the effects of most of the remaining Omicron mutations are not known [16]. Thus, characterising the differences in the clinical presentation of infection by Omicron versus Delta is not only of direct Public Health relevance as the public and clinicians are aware of what symptoms to look out for, but will also assist in understanding the potential effects of future variants of concern.

The current study has several strengths. Key among these, are the one-to-one matched study design, whereby Delta and Omicron infected individuals were matched for age, sex, and vaccination status; the community nature of the study; and the use of a mobile app for daily logging. This has allowed us to assess the duration and severity of acute symptoms in community cases logging prospectively, rather than a biased sample that would be derived retrospectively from a secondary healthcare setting.

We also note some study limitations. First, we were unable to compare symptoms, severity or duration of infection by the two variants in unvaccinated individuals as the majority of study participants were vaccinated. Second, the fact that Omicron and Delta were assigned based on the prevalence in the UK population at the time and not on individual sequencing of the tests from these individuals, and we used self-reported data which can introduce information bias, including misclassification, or effect bias exposure. Although this might theoretically introduce some error, in practice during the time periods selected, over 70% of SARS-CoV-2 sequenced cases by TaqPath laboratories, as reported in daily reports from the UKHSA [17], were either Delta or Omicron which means the error introduced is likely to be small. In addition to the above, some participants might be more likely to report symptoms than others. Furthermore, participants using the app were a self-selected group and not representative of the general population, although we have previously found that our self-reported data aligns well with surveys designed to be representative of the population [18,19]. Fourth, our populations were matched for age, vaccination status and sex but not for any other potential confounders. Fifth, we were unable to assess the role of previous infection on clinical presentation due to insufficient sample size. Sixth, our data are limited by the initial UK vaccine rollout's focus on healthcare workers, the elderly, and clinically vulnerable [20]. Finally, although the study design has matched for vaccination status (two or three

doses), it has not been possible to match for time elapsed since vaccination, with more time being elapsed for Omicron than for Delta. This, however, would likely bias the data in terms of presenting a more severe clinical picture for Omicron than if individuals had been matched for time since vaccination. Therefore, we believe the lack of matching for time since vaccination strengthens the robustness of our key finding, which is that Omicron has a less severe clinical presentation than Delta.

In conclusion, using a matched design we have shown that among vaccinated individuals, the clinical symptoms associated with an infection by the SARS-CoV-2 Omicron variant are different, milder and of shorter duration than those presented by the Delta variant. Furthermore, loss of smell, so totemic in the clinical presentation of COVID-19, is less frequently reported by those infected with Omicron.

Data sharing

Anonymised research data are shared with third parties via the centre for Health Data Research UK (HDRUK.ac.uk). US investigators are encouraged to coordinate data requests through the COPE Consortium (www.monganinstitute.org/cope-consortium). Data updates can be found on https://covid.joinzoe.com

Contributors

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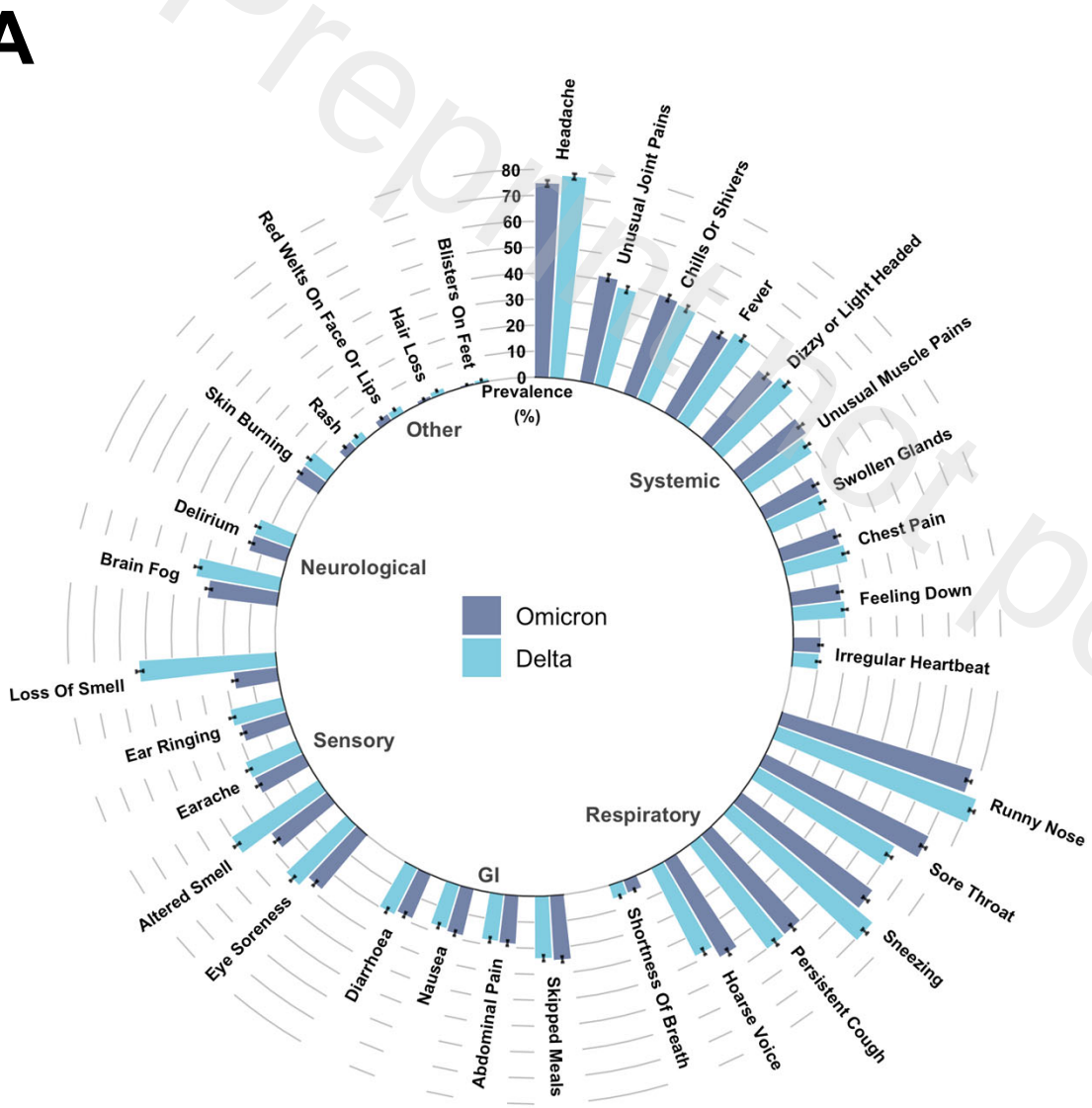
Figure Legends

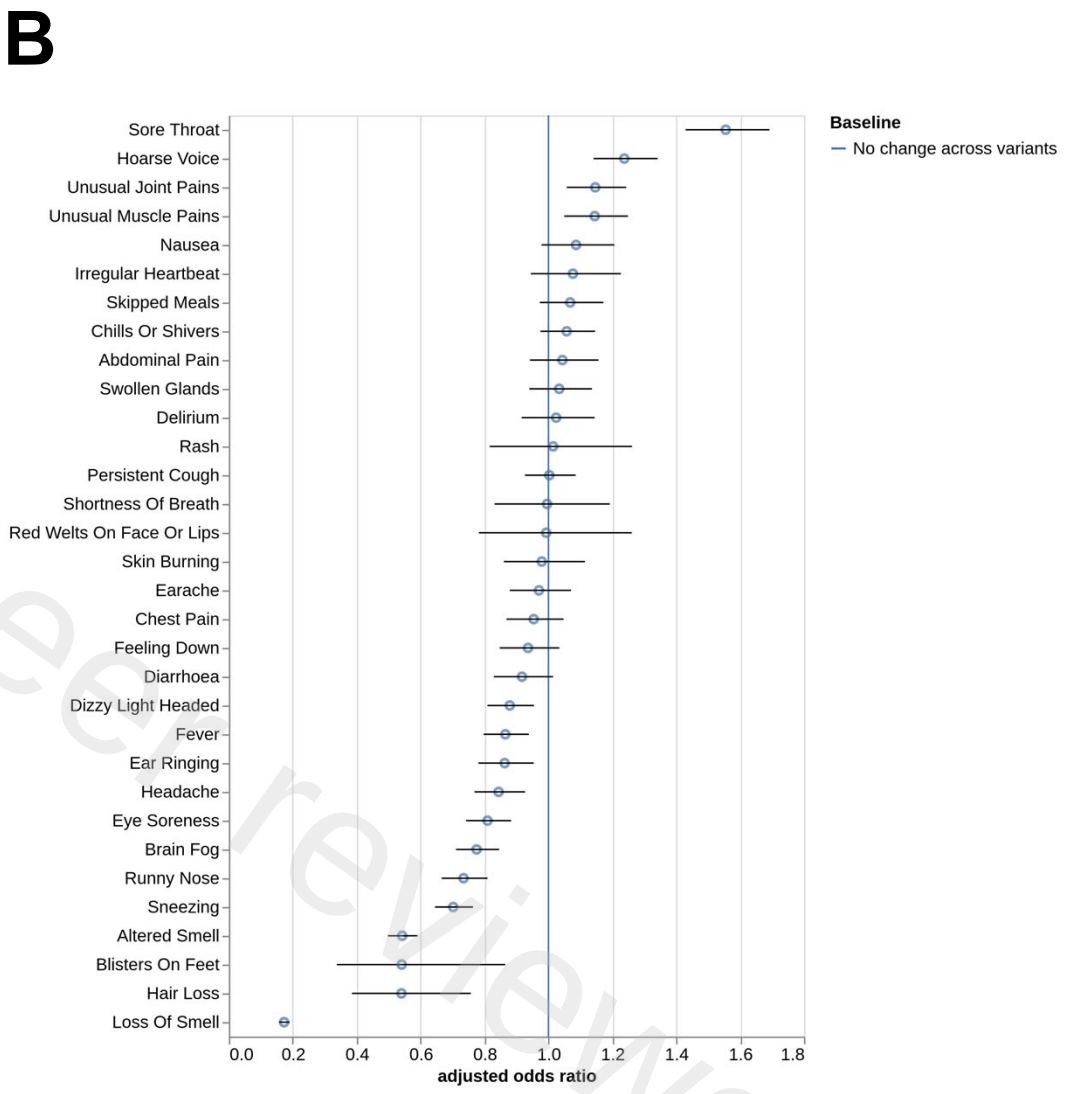
Figure 1. (A) Prevalence of symptoms reported by individuals infected when the Omicron variant (navy) or the Delta variant (blue) was dominant. Average % and 95% CI in the 1:1 matched sample are presented; **(B)** Association between symptoms and COVID-19 infection in 4,990 participants testing positive for SARS-CoV-2 when Omicron was dominant and 4,990 participants testing positive when Delta was dominant. Odds ratio comparing Omicron vs Delta are presented.

Figure 2. (A) Association between type of SARS-CoV-2 infection (Omicron or Delta) and presentation of classical symptoms (defined as at least one among loss of smell, fever, and shortness of breath) in 4,990 participants testing positive for SARS-CoV-2 when Omicron was dominant and 4,990 participants testing positive when Delta was dominant Odds ratio comparing Omicron vs Delta are presented. **(B)** Self-reported hospitalisation and type COVID-19 infection in the same subset as (A). **(C)** Proportion of participants self-reporting symptoms to the ZOE COVID Study app within 21 days after infection with SARS-CoV-2 in the overall matched set and stratified individuals with **(D**) two doses or **(E)** three doses of a COVID-19 vaccine.

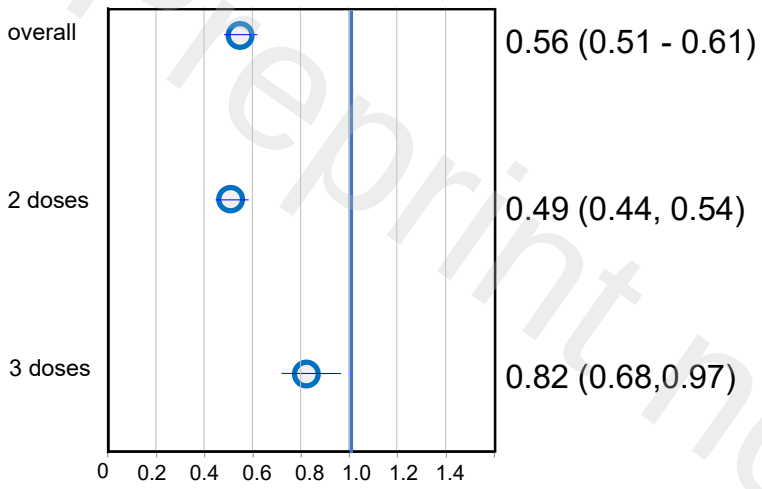
Table 1. Descriptive characteristics of the study population for symptoms and severity; and for duration. Results are presented as (%) for dichotomous traits, and as mean (SD) for continuous traits.

	Overall		1:1 matched sample	
Phenotype	Omicron	Delta	Omicron	Delta
N	29,217	33,785	4,990	4,990
Females, N (%)	18,709 (64%)	2,1296 (63%)	3,302 (66%)	3,302 (66%)
Age, range years	16-98	16-98	16-93	16-93
Age mean (SD) 2 doses	40.35 (14.10)	52.40 (12.19)	40.35 (14.10)	40.58 (13.79)
Age mean (SD) 3 doses	54.84 (13.50)	59.29 (13.27)	59.29 (13.27)	59.29 (13.27)
BMI, kg/m^2	26.62 (5.41)	26.99 (5.55)	26.07 (5.47)	26.3 (5.73)
HCW, N (%)	1922 (7%)	1519 (4%)	256 (5%)	387 (8%)
Comorbidities, N (%)	5309 (18%)	6292 (19%)	638 (13%)	967 (19%)
Second dose, N (%)	3,929 (13%)	3,2724 (97%)	3,929 (79%)	3,929 (79%)
Third dose, N (%)	25,288 (87%)	1061 (3%)	1,061 (21%)	1,061 (21%)
Recovered within 21 days, N	7,139	16,034	1,257	1,257
Average symptom duration	8.06 (4.84)	9.90 (5.14)	6.87 (5.21)	8.89 (5.04)



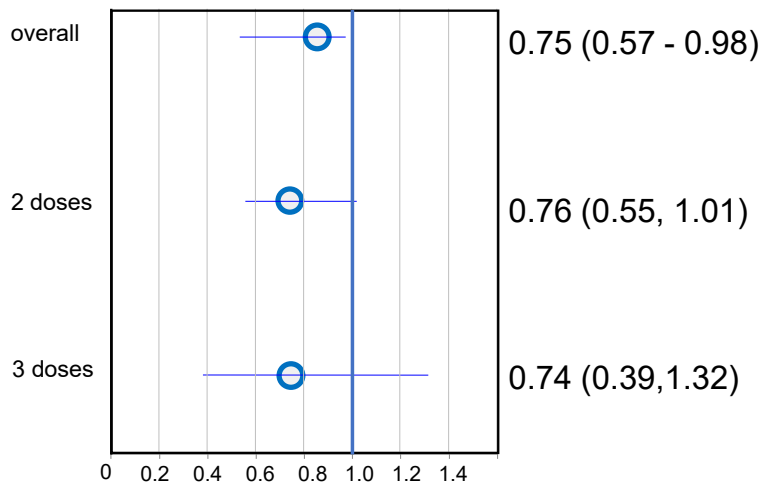


A



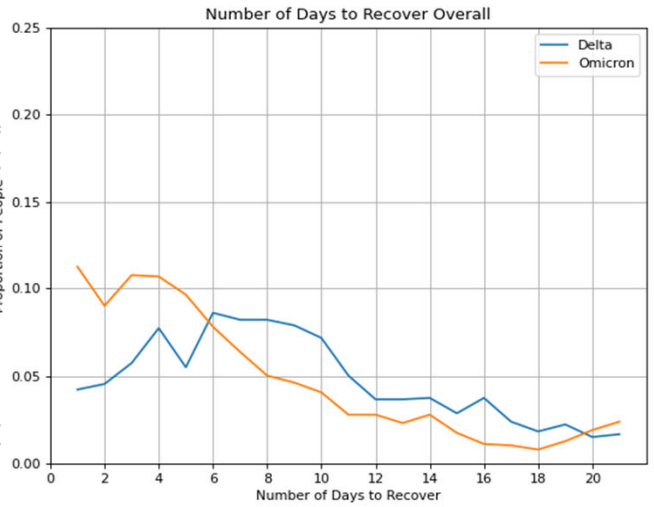
adjusted Odds Ratio (95% CI)
for presenting at least one “classic” symptom
Omicron vs Delta

B

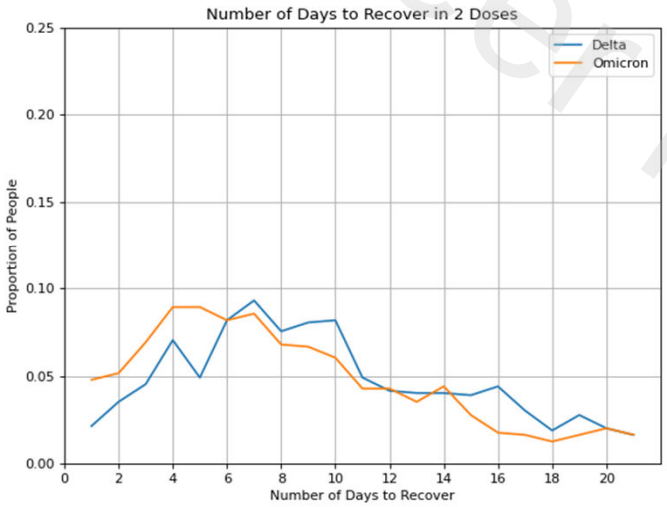


adjusted Odds Ratio (95% CI)
for hospital admission in SARS-CoV-2 Omicron vs Delta infections

C



D



E