Severity and Symptom Characteristics between Omicron and Delta SARS-CoV-2 Variant Infections in the Australian Capital Territory: A Cross-Sectional Study

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Abstract

Background: Despite the widespread dominance of SARS-CoV-2 Delta (B.1.617.2 lineage) and Omicron (B.1.1.529 lineage) variants, there has been little information detailing differences in the presentation of symptoms and clinical characteristics. Characterising symptom and severity profile is important for understanding emerging SARS-CoV-2 variants.

Methods: We conducted a retrospective cross-sectional study of all laboratory-confirmed SARS-CoV-2 infections notified in the Australian Capital Territory (ACT), Australia, between 12 August 2021 and 21 January 2022. Symptom data were ascertained through the initial case investigation interview, and by using either an automated survey or phone interview through routine public follow-up. The routine follow-up for the full isolation period collected individual symptom status and the specific symptoms experienced. We used validated vaccination status through the Australian Immunisation Register (AIR). We used a multivariable logistic regression model to estimate adjusted odds ratios (aOR) for hospitalisation with the Delta and Omicron SARS-CoV-2 variants. We compared the difference in proportions of individual symptoms experienced using Pearson's $\chi 2$ tests, Wilcoxon rank sum test or Fisher's exact tests. We considered results significantly different where p-value was less than 0.05.

Results: We found that a higher proportion of individuals infected with Omicron (32% 144/452) were asymptomatic compared to those infected with Delta (12% 74/613). The most commonly reported symptoms for Delta infections are cough (62%, 381/613), headache (55% 338/613), fever (47% 290/613) and runny nose (47% 289/613). The most commonly reported symptoms for Omicron infections are runny nose (54% 242/452), cough (53% 240/452), sore throat (41% 181/452) and lethargy (39% 176/452). Cases infected with the Omicron variant had a lower odds of hospitalisation compared to cases infected with the Delta variant (OR 0.29, 95% CI 0.16-0.53).

Conclusion: We found that symptom characteristics for Omicron and Delta SARS-CoV-2 infections were significantly different. Furthermore, we found that individuals infected with Omicron were more likely to report no symptoms at all, although vaccination status may have played a role in this cohort.

Overall, infection with Delta was more likely to result in hospitalisation.

Background

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is the virus responsible for COVID-19 (Coronavirus Disease 2019). The World Health Organization (WHO) declared a global pandemic on the 11th of March 2020. Since the first case of SARS-CoV-2 on 12 March 2020, the Australian Capital Territory (ACT), Australia has had three distinct epidemic waves. The second and third waves were the result of community transmission of two SARS-CoV-2 variant of concern (VOC); Delta (B.1.617.2 lineage) and Omicron (B.1.1.529 lineage). Delta was first isolated in India and was designated a VOC on 11 May 2021, and predominated globally until Omicron. Omicron VOC was identified on November 9, 2021 in South Africa; a strain characterised by greater infectiousness and milder clinical course (1). These two strains

have had major international impacts due to their dominance over other well-defined VOCs globally (1,2). In Australia, cases of Omicron increased in all states and territories following the emergence in the country in December 2021 (3).

Australia's surveillance strategy for COVID-19 focused on testing individuals returning from international travel, those with symptomatic disease and people designated close contacts (4). Part of this active surveillance strategy relies on the specific symptoms experienced and their severity (5). The Delta variant is associated with more severe outcomes such as hospital and intensive care unit (ICU) admission compared to previously identified VOCs; Alpha (B.1.17), Beta (B.1.351) and Gamma (P.1) variant infections (6,7). Recent literature suggests that the Omicron variant results in significantly reduction in the odds of hospitalisation compared to other previously identified VOCs (8,9). It is important to characterise and understand the clinical severity of infections based on strain type. In general, COVID-19 in adults predominantly manifests with fever, cough, anosmia, ageusia, dyspnoea, and myalgia, whilst children and young adults are characterised to have mild symptoms or are completely asymptomatic (10-12). Less common symptoms include fatigue, confusion, arthralgia, haemoptysis, anosmia and ageusia but these have been mainly described in previously identified prominent SARS-CoV-2 variants (12-15). Evidence to date show that children infected with SARS-CoV-2 appear to be asymptomatic or display fewer symptoms than adults (7,9). In the absence of active surveillance, such as the lack of testing in people who are either asymptomatic (or in a pre-symptomatic phase; presence of illness before the appearance of symptoms), may lead to an underestimate of the true incidence of SARS-CoV-2 infections (16,17). Furthermore, public health measures such as placing infectious individuals in quarantine may not be effective in slowing the epidemic progression if asymptomatic (or pre-symptomatic) individuals do not seek (16).

Currently, information regarding symptom characteristic and clinical features of SARS-CoV-2 Delta and Omicron infections are scarce. Many studies focus on specific symptoms at the initial case interview, although there have been a few longitudinal and repeated measurement studies of COVID-19 symptoms (13,14). In addition, there is very little data regarding how symptoms present by vaccination status. Describing the symptom characteristics of SARS-CoV-2 variants is not only important for clinicians to assist with early detection of acute infection, but also with informing health risk assessments and potentially reducing the likelihood of severe outcomes (17,18). Furthermore, there are public health benefits more broadly, such as informing appropriate messaging to the public, which in turn has an impact on health resources and respective planning. The aim of our study was to characterise how SARS-CoV-2 Delta and Omicron infections vary in symptomology by sex, age and vaccination status throughout an individual's infection between 12 August 2021 and 21 January 2022, in one of Australia's eight states and territories—the Australian Capital Territory (ACT).

Methods

Study design and data sources

We conducted a cross-sectional study of all laboratory-confirmed SARS-CoV-2 infections notified in the

ACT, Australia, between 12 August 2021 and 21 January 2022. We defined a case as an individual with a throat and nasopharyngeal swab specimen collected and analysed by reverse transcription quantitative polymerase chain reaction (RT-qPCR) by a public health laboratory pathology provider in the ACT. Our inclusion criteria takes into account all confirmed cases managed by ACT Health at the time of notification. Notification data were extracted from a centralised Notifiable Disease Management System. Whole-Genome Sequencing (WGS) analysis were conducted by The Schwessinger Laboratory at the Australian National University (ANU). All cases in this study were confirmed with either Omicron or Delta strain.

Data collection

All data were stored in a Research Electronic Database Capture (REDCap; Vanderbilt University) for surveillance of confirmed COVID-19 cases in the ACT. The inclusion criterion was guided through the definition of a suspected and confirmed SARS-CoV-2 infection outlined by the Communicable Diseases Network Australia (CDNA) Series of National Guidelines for Public Health Units (version 6.4) (18). Public health officers, public health nurses, and epidemiologists collected data using standardised phone interviews. At the time of the data collection, there was a transition from 14-days of mandatory isolation requirement to 7-days. Most Omicron cases were subjected to 7-days of isolation compared to 14-days for Delta cases. The data collected during the initial interview included: demographic characteristics (date of birth and sex), SARS-CoV-2 test results (RT-PCR results), self-reported comorbidities, self-reported symptoms, and hospitalisation status. Hospitalisation status was defined as any admission and include multiple admissions to a private or public hospital in the ACT, Australia within an infected individual's active follow-up period. Hospitalisation status was validated by the Clinical Health Emergency Coordination Centre (CHECC). Comorbidities were defined as any identified health conditions that may place an individual at risk of severe complication which includes any one or more of the following conditions: asthma, immunosuppression condition/therapy, renal disease, diabetes, hypertension, liver disease and/or neurological disorder. The questionnaire included binary fields (yes or no questions) regarding specific symptoms experienced: fever, cough, dyspnoea, malaise, fatigue, loss of taste and/or smell, sputum/respiratory secretions, headache, sore throat, shortness of breath (defined as the subjective perception of shortness of breath or difficulty of breathing by the patient), myalgia, rhinorrhoea, chills, diarrhoea, vomiting and "other". The "other" option designates a free text field whereby other symptoms that were not listed could be described and collected. If a case is less than 18 years of age, the standardised phone interview and survey was conducted with or in the presence of a parent or guardian. After the initial interview, all of the cases were followed up using either an automated survey or phone interview on a daily basis for the full duration of their isolation period that collected information regarding their symptom status (whether any symptoms were experienced at the time of survey) and specific symptoms experienced. Isolation period was defined as the date for when a case entered self-isolation until they were cleared by medical and public health professionals of ACT Health's Public Health Emergency Coordination Centre (PHECC), defined by the national guidelines. During the study period in January 2022, rather than conducting phone interviews for all laboratory detected SARS-CoV-2 infection,

the ACT shifted focus on managing high risk and sensitive sites and individuals that may be affected by COVID-19.

Vaccination Status

Public health staff conducted a validation procedure for an individual's vaccination status at the time of infection through a population-wide vaccination register—the Australian Immunisation Register (AIR). Vaccination status was defined as: (i) Unvaccinated: individuals who had not received any doses of a SARS-CoV-2 vaccine received or 1 dose receive with less than 14 days between diagnosis date; (ii) Partially vaccinated: individuals who have had only 1 dose received 14 days after diagnosis date, or 2 doses with less than 14 days between a diagnosis date and the second dose was received; and (iii) Fully vaccinated: individuals who had received 2 doses with more than 14 days between diagnosis date and second dose received which included a third dose, if applicable. The COVID-19 vaccine doses that were approved for use at the time of investigation is one dose of COVID-19 Vaccine Janssen (Johnson & Johnson, New Brunswick, United States) for a full coverage, or two doses of Comirnaty (Pfizer/BioNTech, Mainz, Germany/New York, United States), Vaxzevria (AstraZeneca, Cambridge, United Kingdom), Spikevax (Moderna, Cambridge, United States).

Statistical Analysis

We analysed a de-identified line-list of data was analysed using Stata Statistical Software, Release 17 (College Station, TX: StataCorp LLC) and R, version 4.1.0, statistical software (R Foundation for Statistical Computing, Vienna, Austria) (20,21). Categorical data were presented as frequency and proportions. Continuous variables were described using mean, SD, median, range and interquartile range (IQR). We compared the difference in proportions using Pearson's χ^2 tests, Wilcoxon rank sum test or Fisher's exact test.

Demographic data were presented as descriptive statistics. Age was collected as a continuous variable, but categorical aged-groups were applied. We compared SARS-CoV-2 Delta variant infections (where only Delta was present in the ACT) notified between August 12 and 30 September 2021, with cases sequenced with the Omicron variant between 1 December 2021 and 21 January 2022 (where all confirmed Delta cases were excluded). Univariable analysis was conducted, and all variables with *p* less than 0.25 was included in the final multivariable logistic model. We conducted multivariable logistic regression to examine the association of different variant infections with hospitalisation as a proxy for disease severity. We used a multivariable logistic regression model to estimate an adjusted odds ratio (aOR) for hospitalisation across all SARS-CoV-2 infections. The results were considered statistically significant where was *p* is less than 0.05.

Results

Demographic Characteristics

From 12 August 2021 to 21 January 2022, there was a total of 1065 confirmed cases that met the inclusion criteria for this study. Of these cases, 58% (613/1065) returned a genomic sequencing result

with the Delta variant, with the remainder being the Omicron variant. Overall, the median age of cases was 28 years (range: 0 months to 95 years), with individuals infected with a Delta infection generally younger (median = 28, *SD* = 17 years) compared to cases infected with the Omicron variant (median = 31, *SD* = 15 years). Most cases were aged between 18–39-year-old age-group (54% 575/1065).

Overall, 51% (545/1065) of cases were male. Data regarding vaccination status was available for all cases in the study. Only 19% (118/613) of cases infected with Delta were fully vaccinated, which was significantly different to those infected with Omicron (85% 385/452) within the cohort. Overall, 21% (223/1065) of cases reported at least one comorbidity, which was similar for Delta and Omicron cases (Table 1).

Clinical Characteristics

In total, 6.6% (70/1065) of all cases were hospitalised, with 77% (54/70) of these being not fully vaccinated. Ten per cent (7/70) of hospitalised cases were partially and 13% were fully vaccinated (10%, 7/70 and 13%, 9/54). The crude proportions of cases hospitalised was lower for Omicron (9%, 57/613) than Delta (3%, 13/452). Of all cases admitted to the hospital, a small number of patients were admitted to the ICU (11% 8/70). A total of 43% (3/7) of these patients required oxygen support through mechanical ventilation whilst admitted in ICU. All cases admitted to ICU and subsequently requiring ventilation support due to COVID-19 complications were infected with the Delta variant (Table 1). There were no reportable deaths within the study period.

Symptom Characteristics

Overall, 80% (847/1065) of cases reported at least one symptom during their follow-up period. A higher proportion of individuals infected with Omicron were asymptomatic (32%, 144/452) compared to those infected with Delta (12%, 74/613) (Table 2). The vaccination status for the 0–12-year group did not differ, therefore we deemed it appropriate to compare proportions of each individual symptoms. Headache, fever, joint pain, shortness of breath and chest pain were more predominant with Delta than Omicron (Figure 1). The presence of abdominal pain, sore throat, runny nose and cough were similar across the 0–12-year age group. The most commonly reported symptoms for Delta infections were cough (62%, 381/613), headache (55%, 338/613), fever (47%, 290/613) and runny nose (47%, 289/613). The most commonly reported symptoms for Omicron infections were runny nose (54%, 242/452), cough (53%, 240/452), sore throat (41%, 181/452) and lethargy (39%, 176/452). Fever, nausea and loss of taste or smell was more prominent in the 0-12 year group for Delta infections compared to cases with Omicron (Figure 1). There were distinct symptoms that were significantly different in proportion between Delta and Omicron variant infections, including: fever, cough, runny nose, headache, lethargy, myalgia (muscle pain), joint pain, diarrhoea, nausea/vomit, loss of taste or smell and night sweats (Figure 2). Overall, lethargy is the only symptom that was significantly more common in proportion in Omicron infected individuals compared to those infected with Delta (Figure 3). The median number of symptoms reported was higher for cases infected with Delta (median=4, IQR=2-7) compared to cases infected with Omicron (median=3, IQR=0-6).

Regression analysis results

In multivariable logistic regression people aged 40-59 years (aOR 3.01, 95% CI 1.29-7.03 $p<0.05$) and over 60 years (aOR 5.95, 95% CI 1.53-16.67 $p<0.05$) had higher odds of hospitalisation (Table 2). People who were unvaccinated (aOR 6.38, 95% CI 3.32-27.46 $p<0.01$) had significantly higher odds of hospitalisation. The regression results indicate that cases with the Omicron variant infection had a lower odds of hospitalisation (OR 0.29 95% CI 0.16-0.53 $p<0.01$) compared to cases infected with Delta variant independent of vaccination status, although the results were uncertain as it was not significant when adjusted.

Discussion

Our study highlights that infection with Omicron is less likely to result in hospitalisation and manifests in different symptoms when compared to and clinical characteristics between Omicron and Delta SARS-CoV-2 infections with Delta, even after accounting for vaccination status. This was at the time where there was a major transition of strain dominance from Delta to Omicron in the ACT.

In our study, the majority of SARS-CoV-2 infections (80%) reported symptoms within their follow-up period. Consistent with other research, we found that individuals infected with the Omicron variant were more likely to be asymptomatic compared to Delta infections (21,22). Individual symptoms that were less prominent in individuals infected with an Omicron infection were; fever, cough, headache, muscle pain, joint pain, diarrhoea, nausea/vomit, loss of taste or smell and night sweats. Recent literature has described the propensity for different variants to infect different cells in the respiratory tract (23,24). It has been observed that individuals infected with the Omicron variant enter cells differently compared to Delta infections (25). Furthermore, it has been shown that there is lower viral replication in the lungs (23). This may explain the lower propensity of respiratory symptoms, such as cough, sore throat and runny nose, with Omicron infections compared with other SARS-CoV-2 variants (5,12,26). Lethargy was the only symptom that was significantly more common in proportion in Omicron infected individuals compared to those infected with Delta. Cough, sore throat and runny nose were prominent across all age-groups irrespective of vaccination status (Figure 3). It should also be noted that diarrhoea, abdominal pain, loss of smell and taste were reported to be present across all age-groups in the unvaccinated Delta variant cohort compared to the Omicron variant group that consisted of mostly fully vaccinated individuals. There were no significant differences between symptom presentation by sex.

We found that individuals infected with the Omicron variant had lower odds of being hospitalised than those with a Delta variant infection. In addition, older (specifically, 40-59 and over 60 year) age-groups and unvaccinated cases had higher odds of hospitalisation which supports current evidence (27,28). We observed significantly different self-reported symptoms reported by cases infected with the two variants. In addition, the results show that there was a significantly higher total of individual symptoms reported with the Delta variant compared to Omicron variant infections. Since Australia's current surveillance strategy continue to rely on testing symptomatic individuals, there must remain a focus on public messaging regarding specific symptoms experience (with or without exposure to a COVID-19 case) (5).

This is one of the key importance of this study, it will give clinicians insight into symptoms that may be indicative of COVID-19.

A key strength of the study is that we followed up cases prospectively until they were cleared under public health requirements. This meant that we could collect data on individual symptoms that may have been experienced later in the infection, compared to other studies that captured information at the initial case investigation interview. Another strength of this study is that we used validated information regarding vaccination status for COVID-19 for Australian residents. This allowed for a more accurate representation of the cohort compared to using self-reported vaccination status. It is important to note that all SARS-CoV-2 variants have the potential to cause severe disease, especially vulnerable populations. We also defined cases by WGS confirmation, compared to other studies that utilise period of time where one strain is predominant compared to another time period (26). Understanding the associations between the number of symptoms, specific groupings of symptoms, vaccination status, and its influence on clinical outcomes may have merit in the reduction (and prevention) of severe outcomes (14,15,26,29). The rapid detection and characterization of new and emerging SARS-CoV-2 variants is imperative in informing public health and control measures, and decision making that has the potential to impact health care systems (29,30).

Self-reported data can be subject to recall and misclassification bias. Consideration must be taken when interpreting reported symptom and comorbidities. Further to recall bias, many children (aged 17-years or below) may have had their parent/s or guardian conduct the interview or survey questionnaire on their behalf and may not have been able to articulate the range of symptoms that were (or were not) experienced. As previously outlined, rather than conducting phone interviews for all laboratory detected SARS-CoV-2 infection, the ACT shifted focus on managing high risk and sensitive sites and individuals that may be affected by COVID-19. This meant that confirmed cases were provided with an online questionnaire rather than the full extent of a phone interview, and was not applied to the majority of notified cases from January 2022 onwards. This may have influenced the detail collected for each case record. Another limitation is that we only considered whether an individual had any pre-existing health or medical condition present rather than specific (or delineated between) acute and/or chronic conditions. Risk factors such as diabetes, prior cardiac or pulmonary disease have been associated with worse prognosis (31,32). The inclusion whether an individual has had any pre-existing conditions was a significant variable that influenced the multivariable logistic regression analysis. Future studies could investigate the interaction between specific health or medical condition with symptomology of COVID-19 patient (30,33). Lastly, vaccinated cases in the Delta group account for a small proportion overall within the study cohort. This may not be generalisable due to the high vaccination rates in the ACT at the time of the investigation. This was due to the limited vaccine eligibility and uptake (between August and November 2021) of cases included in the study. This reflects why most of the SARS-CoV-2 Delta infections were unvaccinated. Furthermore, waning vaccine-derived immunity have been a contributing factor to the increase in Omicron infections during the study period (34,35).

Conclusion

We describe how SARS-CoV-2 Delta and Omicron variant infections differ in their presentation of explicit symptoms within an individual's full public health follow-up period. The result of this analysis has given further weight to existing evidence that Omicron variant infections are less severe than those of Delta infections and present with different symptoms. The rapid detection and characterisation of new and emerging SARS-CoV-2 variants are imperative in informing public health and control measures. Moving forward, the focus will continue in addressing waning immunity through booster vaccine doses, development of multivalent vaccines and active surveillance within high-risk settings. Public health measures such as social distancing and mask use will still need to be in the forefront of the publics' mind.

Abbreviations

AIR: Australian Immunisation Register; CDGN: Communicable Disease Genomics Network; CDNA: Communicable Diseases Network Australia; CHECC: Clinical Health Emergency Coordination Centre; COVID-19: Coronavirus Disease 2019; ICU: Intensive Care Unit; OR: Odds Ratio; PHECC: Public Health Emergency Coordination Centre; REDCap: Research Electronic Database Capture; RT-qPCR: reverse transcription quantitative polymerase chain reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2.

Declarations

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Ethical Considerations

All methods were carried out in accordance with the *Public Health Act 1997* for the purpose of a public health investigation and system quality improvement protocol. All experimental protocols, consent and data collection were conducted under the guidelines and regulation of the *Public Health Act 1997* (Division 6.2, Section 109). Ethics approval and consent to participate was deemed unnecessary according to national regulations. Approval of research and data release was approved by the data custodian of public health investigations in the Australian Capital Territory under the *Public Health Act*

1997. As this was a retrospective study, all data used was considered and approved by the Chief Health Officer, ACT Health Directorate.

Consent for publication

Not applicable

Competing interests

The authors declare no competing interests

Availability of data and materials

The datasets generated and/or analysed during the current study are available from ACT Health on reasonable request.

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Author's contributions

AG, MDK, MK and TSG conceived and designed the study. AG and TVV contributed to acquisition, statistical analysis and interpretation of the results. All authors critically reviewed and provided intellectual input for preparing the manuscript. All authors read and approved the final version of manuscript submitted for publication.

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Figures

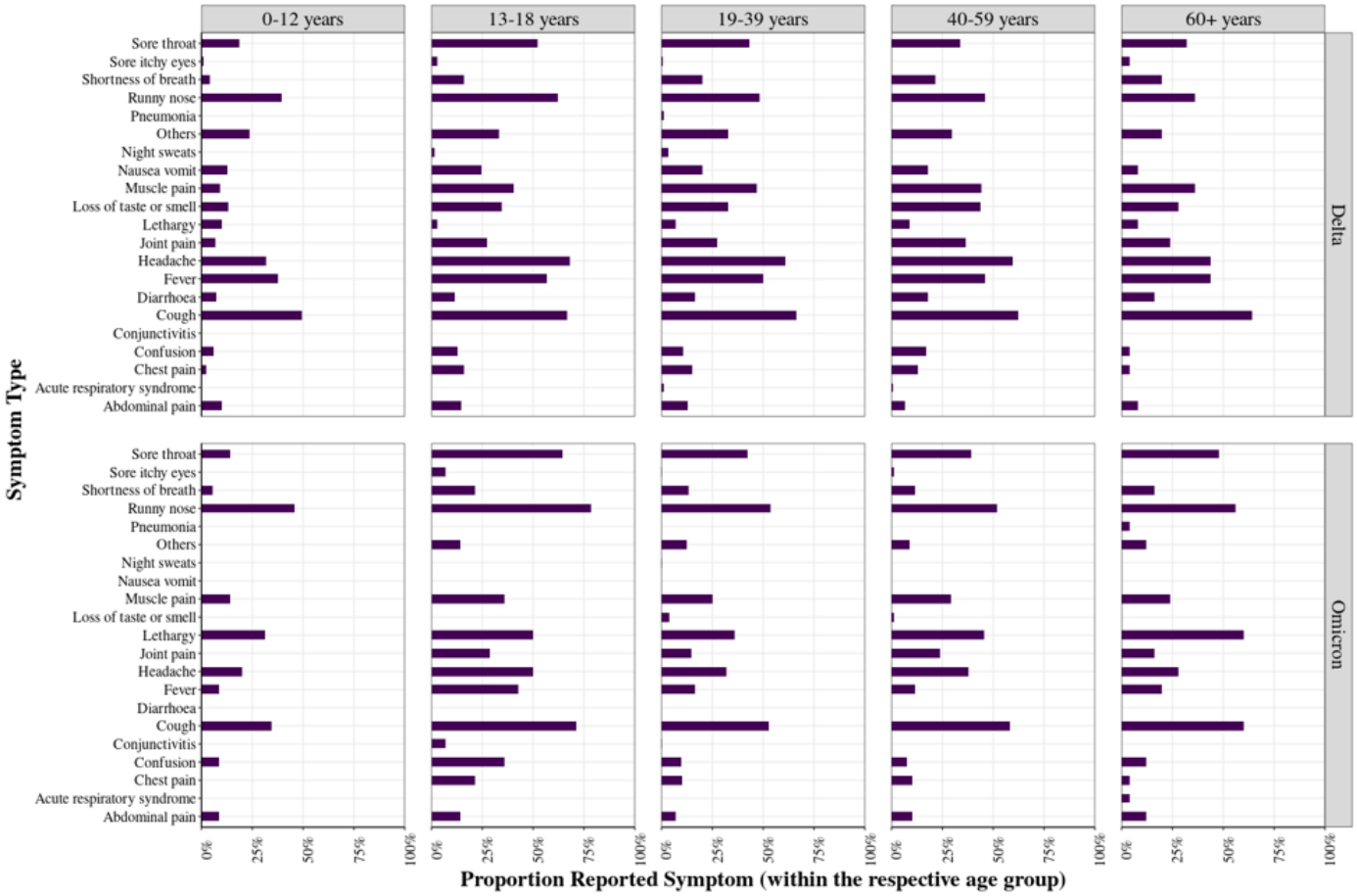

Figure 1

Distribution of reported symptoms, age-group (years) by SARS-CoV-2 variant (Omicron or Delta) - Australian Capital Territory, 12 August 2021 to 21 January 2022.

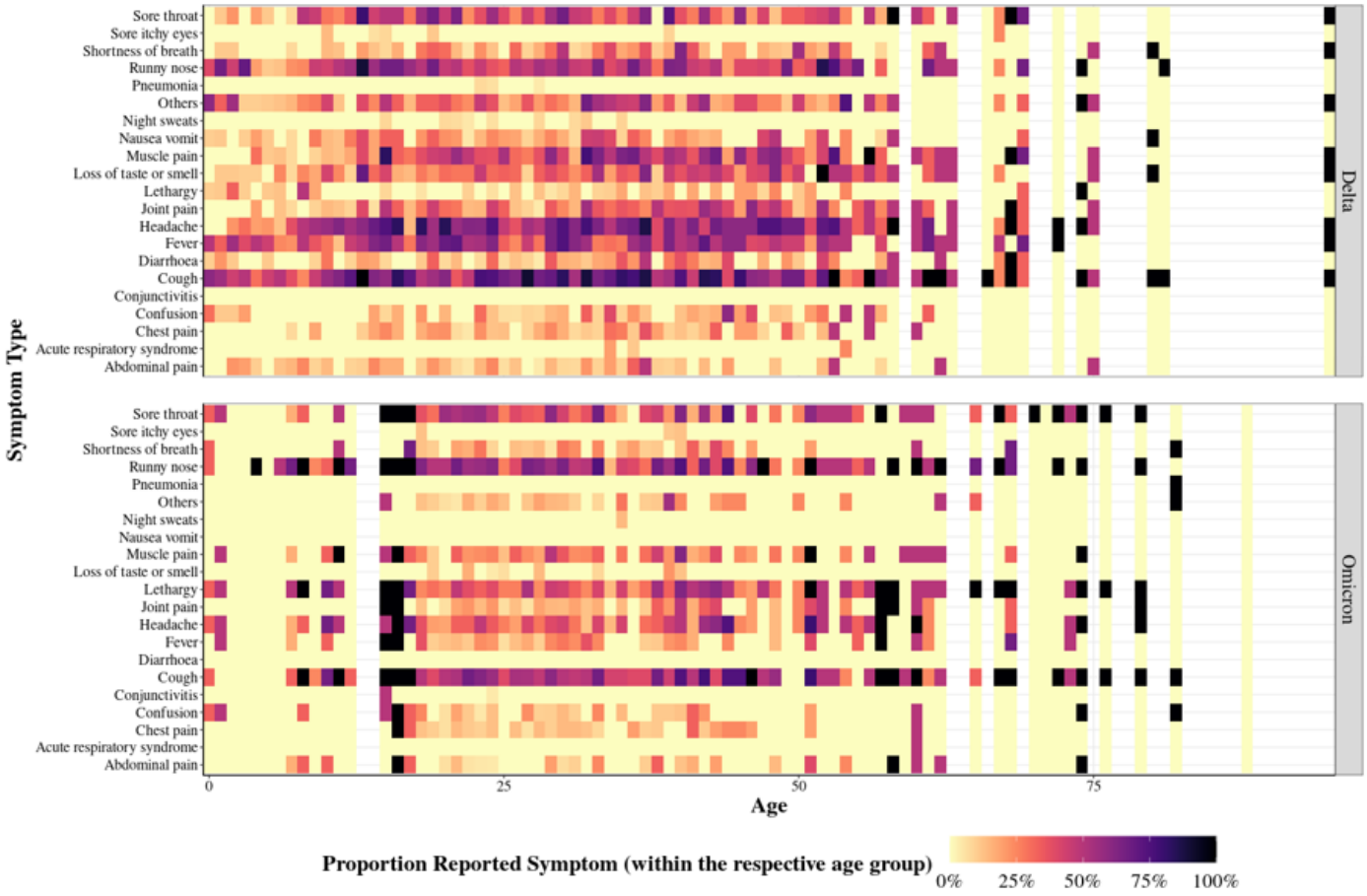

Figure 2

Heatmap distribution of reported symptoms, age (years) by SARS-CoV-2 variant (Omicron or Delta) - Australian Capital Territory, 12 August 2021 to 21 January 2022.

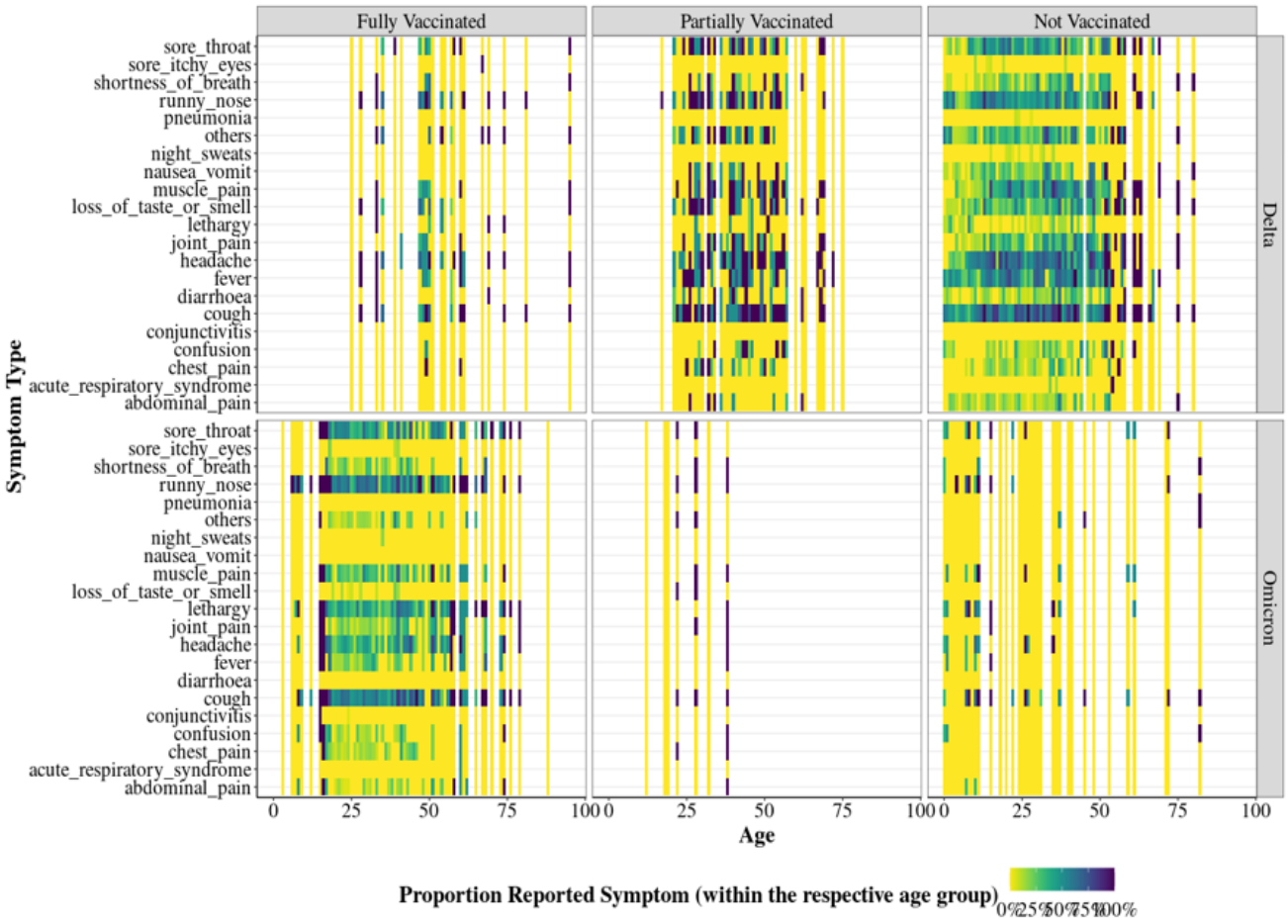

Figure 3

Heatmap of the proportion of reported symptoms by vaccination status and SARS-CoV-2 lineage type (Omicron or Delta).

Supplementary Files

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- Tables.docx
- Appendices.docx