International Severe Acute Respiratory and emerging Infections Consortium

A global federation of clinical research networks, providing a proficient, coordinated, and agile research response to outbreak-prone infectious disease

Analysis Plan for ISARIC International COVID-19 Patients

Title
Characterising SARS-CoV-2 Omicron vs Delta variant in terms of vaccination status, clinical presentation and outcomes
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Introduction

This document outlines the analyses planned to characterize the clinical presentation and severity of infection by the SARS-CoV-2 Omicron variant (henceforth Omicron variant). As of 1 December 2021, more than 300 cases of the SARS-CoV-2 Omicron variant of concern (VOC) have been identified in 27 countries,(1) representing a potential threat to pandemic control efforts. To provide key information for public health response, this analysis aims to assess whether disease caused by the Omicron variant differs in terms of severity and vaccine efficacy against hospitalisation compared with the currently dominant Delta (B.1.617.2) variant.

This work will involve analyses of prospectively collected data by ISARIC partners, in particular data on infecting variant.

Participatory Approach

All ISARIC partners contributing data to the ISARIC Data Platform from 01NOV21 onwards are invited to participate in this analysis through review and input on the statistical analysis plan and resulting publication. The outputs of this work will be disseminated as widely as possible to inform patient care and public health policy, this may include submission for publication in an international, peer-reviewed journal. The names of all those who contribute data to this analysis will be included in all outputs as cited authors or collaborators per ICMJE policies and the ISARIC publication policy.

Research Plan

Summary of Research Objectives

Primary objectives:

1. To estimate the association between vaccination status and hospitalization with Omicron variant, relative to hospitalization with Delta variant
2. To characterise the severity of clinical presentation and outcomes in hospitalized patients with Omicron variant, relative to hospitalized patients infected with Delta variant

Secondary objectives:

1. To characterise the clinical profile of patients infected with Omicron variant compared to patients infected with Delta variant
2. To estimate the prevalence of comorbidities in hospitalized patients infected with Omicron variant and compare with patients infected with Delta variant
3. To estimate the associations of age, sex, symptoms, comorbidities, and treatments with risk of unfavourable outcome (death or invasive mechanical ventilation, IMV) in hospitalized patients with Omicron and Delta variants

Proposed Target Population

All COVID-19 hospitalised cases known to be caused by Delta or Omicron variant. In particular, identification of SARS-CoV-2 variants will be required by means of one of the following methods: genome sequencing, S-gene target failure (SGTF), or genotyping.

Clinical Questions/Descriptive Analyses

1. Are there differences in vaccination status in hospitalised cases caused by Delta and Omicron variants? - I.e., is there a difference in the odds of having been previously vaccinated between patients being hospitalised with COVID-19 caused by the Omicron vs the Delta variant?
2. Are the risks of unfavourable outcomes (death or invasive mechanical ventilation, IMV) and the related risk factors, different between hospitalised patients infected with Omicron and Delta variants?

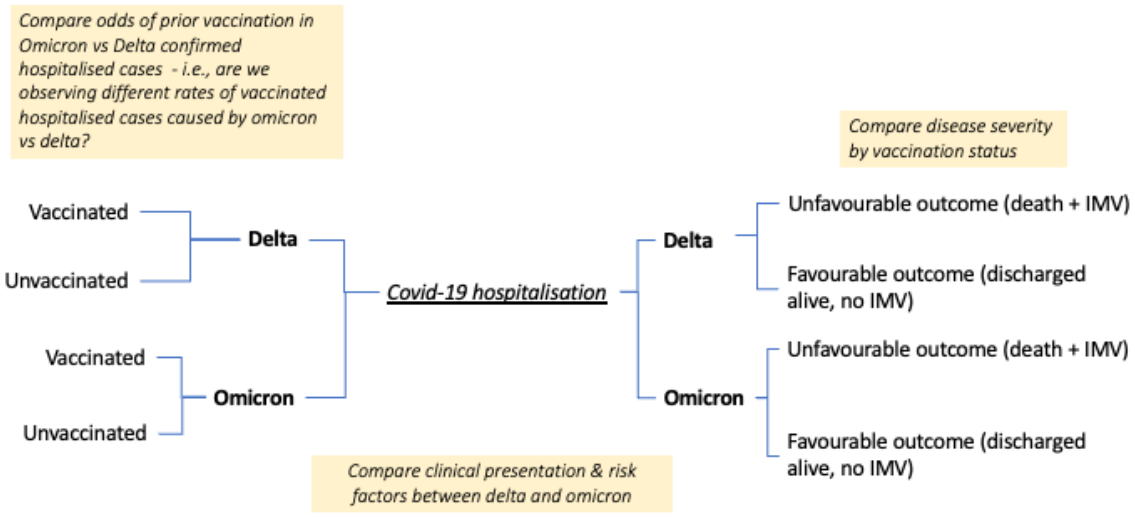
3. Are presenting clinical profiles and patient characteristics different for hospitalised COVID-19 cases caused by the Omicron and Delta variant?

Planned Statistical Analyses, Methodology and Representation

General approach

The emergence of the Omicron variant is occurring in a context of increasing vaccine coverage in several countries, and consequently of changing levels of immunity in the population. To provide more robust answers to the clinical questions described above we will prioritise inclusion, in the analyses described below, of data collected prospectively from November 2021. This will ensure that systematic differences between Delta and Omicron infected patients linked to temporal changes in preventive and therapeutic interventions are minimised.

The overall design is summarised below:



Assessment of association between vaccination status and SARS CoV2 variants

A key question to address is whether vaccines are equally effective against Omicron and Delta variant hospitalisation. When test-negative controls are available, vaccine effectiveness studies can be, and have been, conducted when a new COVID-19 variant emerges. However, even in the absence of test-negative controls, a case-case (here Delta versus Omicron variant) design can be used to evaluate the

frequency of previous vaccination between cases presenting with different variants. Whilst our study population will only include hospitalised cases with confirmed SARS-CoV-2 and hence direct estimation of vaccine effectiveness is not possible, we will estimate the relative frequency of previous vaccination in patients infected by Omicron variant versus Delta variant, which will provide an indication on the comparative effectiveness of the vaccine on these two variants.

Comparison: We will compare the frequency of previous vaccination in hospitalized patients infected with Omicron variant and Delta variant.

Statistical approach: Logistic regression will be used to estimate the associations of vaccination (and vaccination regimen) with variant. Previous observational studies assessing vaccine effectiveness have identified several factors that might confound this association, such as age, comorbidities, calendar time (e.g., week), ethnic group, which will be adjusted for. Analyses will be done within countries and if appropriate data will be pooled, with a fixed or random (intercept) effect for country, depending on the number of countries included, to account for variation in vaccine coverage. Importantly, as shown by Bernal et al,(3) vaccine effectiveness depends on the number of doses and time since vaccination. For this reason, we will also estimate associations by vaccination regimen.

In the table below, we present required sample sizes for this analysis (power = 80%, alpha = 0.05), for a range of assumptions on the frequency of previous vaccination in Delta variant-infected patients and association levels (i.e., assumed odds ratio [OR]). These sample size calculations should be interpreted as providing guidance on the order of magnitude as ratio between numbers of Delta and Omicron variant hospitalized cases will change dynamically with time.

Proportion of delta cases who are vaccinated	Odds ratio for association of previous vaccination and omicron variant (vs. delta)	Ratio Delta : Omicron hospitalised cases	Number of Omicron hospitalized cases required	Number of Delta hospitalized cases required
0.4	0.8	0.5	2031	1016
0.4	0.8	1	1349	1349
0.4	0.8	2	1008	2016
0.4	1.2	0.5	2901	1451
0.4	1.2	1	1938	1938
0.4	1.2	2	1456	2912
0.4	1.4	0.5	844	422
0.4	1.4	1	564	564
0.4	1.4	2	424	848
0.4	1.6	0.5	431	216
0.4	1.6	1	288	288
0.4	1.6	2	217	434
0.6	0.8	0.5	1931	966
0.6	0.8	1	1290	1290
0.6	0.8	2	970	1940
0.6	1.2	0.5	3023	1512
0.6	1.2	1	2010	2010
0.6	1.2	2	1503	3006
0.6	1.4	0.5	910	455
0.6	1.4	1	604	604
0.6	1.4	2	450	900
0.6	1.6	0.5	479	240
0.6	1.6	1	317	317
0.6	1.6	2	235	470
0.8	0.8	0.5	2750	1375
0.8	0.8	1	1850	1850
0.8	0.8	2	1399	2798
0.8	1.2	0.5	4722	2361
0.8	1.2	1	3125	3125
0.8	1.2	2	2326	4652
0.8	1.4	0.5	1470	735
0.8	1.4	1	967	967
0.8	1.4	2	714	1428
0.8	1.6	0.5	794	397
0.8	1.6	1	520	520
0.8	1.6	2	381	762

In addition to assessing the association between vaccination status and SARS-CoV-2 infecting variant, we will also assess whether the protective effect of vaccination on disease severity of hospitalised patients differs for Omicron and Delta variants (i.e., whether there is modification of the association between vaccine status and severe outcomes by infecting variant). The outcomes and statistical approach that will be used to address this question are described in the next subsection.

<u>Characterising disease severity in hospitalized patients with Omicron versus Delta variant</u>

There is epidemiological evidence that disease severity can vary in patients infected with different SARS CoV2 variants.(4) Currently no data are available on the clinical outcomes of hospitalised patients infected with Omicron variant. In this subsection, we will describe analyses that will be performed to describe the relative severity of Omicron versus Delta variant.

Outcomes: The primary outcome in this analysis is a composite outcome that consists of invasive mechanical ventilation or death. Secondary outcomes include death, admission to intensive/high-dependency care unit and length of hospital and ICU length of stay. The primary analysis will include the first 14 days after hospital admission, after which patients will be censored; secondary analyses will assess

outcomes occurring in the first 28 days after admission and tertiary analyses will assess outcomes occurring in the first 90 days after admission.

Statistical approach: Cumulative incidence curves of death and discharge (and ICU and IMV) will be plotted for hospitalized patients with Omicron variant infection and patients with Delta variant infection. Cox proportional hazards models will be fitted, amending censoring times of discharged patients, adjusting for age, sex, vaccination status, number of comorbidities and other potential confounders, and stratifying by country. The proportional hazards assumption will be checked.

As mentioned in the previous subsection, survival analyses will also be performed to assess the association of vaccination with severe outcomes in hospitalized patients. Following guidance on presentation of effect modification analyses, analyses will be performed for patients infected with Omicron variant and Delta variant separately, as well as include a multivariable model to test for multiplicative interaction.(5)

Below we present a table that includes required numbers of patients to have 90% power to detect a range of hazard ratios of the outcome (death or the composite outcome of death/IMV) (assuming that 25% of hospitalised patients experience the outcome) between patients infected with Omicron and Delta variants.

	Hazard ratio					
Proportion with Omicron	0.5	0.75	1.25	1.5	1.75	2
0.1	972	5643	9379	2841	1491	972
0.2	547	3174	5276	1598	839	547

0.3	417	2418	4019	1217	639	417
0.4	364	2116	3517	1065	559	364
0.5	350	2031	3376	1023	537	350

These sample size calculations are only an indication of the approximate number of individuals needed for a simplified version of each type of analysis.

Symptom profile and concomitant medical conditions in hospitalised patients infected with Omicron and Delta variants

Two key components of the clinical research response to the emergence of the Omicron variant will be: (1) description of symptoms in hospitalised patients infected with this variant, and whether there are differences compared to other circulating variants, in particular Delta variant; (2) whether hospitalised patients with the new variant have a similar history of medical conditions or comorbidities to that of patients infected with other variants.

Outcomes: Frequent symptoms and comorbidities will be compared between hospitalised patients infected with Omicron variant and patients infected with Delta variant.

Statistical approach: Comparative plots will be generated with frequencies of symptoms and with frequencies of comorbidities. If appropriate, depending on region-specific sample size, region-specific plots will also be created to assess regional differences in presentation. Frequent symptoms (fever, cough, shortness of breath, fatigue) and comorbidities (hypertension, diabetes, obesity, smoking) will be compared between variants using logistic regression models, with adjustment for age and sex, and accounting for country, either as a covariate or random intercepts, depending on number of countries included in the analytical dataset.

Handling of Missing Data
Missingness in the data will be assessed for all variables, by region and calendar month. This will enable the identification of variables that lack sufficient data to allow for robust analysis and might inform the likely missingness mechanism. Types of missingness will be considered including whether data are not missing at random and follow-up with sites will be conducted if appropriate. Variables with greater than 30% missingness will be excluded from analysis. If appropriate, imputation will be performed using Multiple Imputation by Chained Equations (MICE); complete case analysis will also be performed, as sensitivity analysis.

Other Information

Data collected in the ISARIC CORE and RAPID databases will be analysed and shared rapidly and regularly with ISARIC Partners and the global community to inform planning and patient management. This is a targeted approach which we aim to complete within 3 months depending on transmission and recruitment, while we experience co-circulation of delta and omicron.

References

1. European Centre for Disease Prevention and Control. Threat Assessment Brief: Implications of the further emergence and spread of the SARS CoV 2 B.1.1.529 variant of concern (Omicron) for the EU/EEA first update [Internet]. European Centre for Disease Prevention and Control. 2021 [cited 2021 Dec 4]. Available from: https://www.ecdc.europa.eu/en/publications-data/covid-19-threat-assessment-spread-omicron-first-update

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