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
Comparing clinical presentation and outcomes of hospitalised SARS-CoV-2 patients before and after the spread of the Omicron variant
Version: (Date: Day/Month/Year)
13th December 2021
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Introduction

As of 9 December 2021, the Omicron variant of concern (VOC) had been identified in 63 countries, (1) representing a potential threat to pandemic control efforts. Thus far, only limited data are available on the clinical characteristics of infections caused by this variant. This document outlines analyses planned to characterize changes in hospitalised patient population (e.g. age, sex, ethnicity) and in clinical presentation and disease severity before versus after the spread of SARS-CoV-2 Omicron variant (henceforth Omicron variant). Data on population-level frequency of the Omicron variant, relative to the Delta variant, will be used to define comparison groups (i.e. infections likely to have been caused by the dominant variant at the community-level). Our overarching aim is to inform public health responses by combining available population-level data on relative frequencies of different variants and individual-level clinical data on hospitalised cases.

This work will involve analyses of prospectively collected data by ISARIC partners, from November 2021 to February 2022, and, where available, previously and recently collected data during a period where Delta variant dominates, which might vary between countries. The latter will provide information on baseline clinical characteristics of COVID-19 hospitalised patients before the emergence of the Omicron variant. In addition to detailed data on in-hospital clinical course, population-level data on the relative frequencies of different SARS-CoV-2 variants (e.g. percentage of weekly clinical cases caused by Omicron variant) will be used in this analysis. Whilst ISARIC partners will be encouraged to identify potential sources that could provide relevant community-level data on variant frequency, community-level data will be collated in collaboration with Global.health. Although not a requirement for analyses described in this document, population-level data on vaccination coverage will also be used where available.

We will also apply the methods proposed in this SAP to data relating to the emergence of other SARS-CoV-2 variants, for which there are more robust descriptions of variant-specific clinical characteristics and outcomes. The rationale is to validate this approach by comparing inferences with published studies using other designs.

Participatory Approach

All ISARIC partners contributing data to the ISARIC Data Platform from 01 November 2021 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 compare disease severity in hospitalized patients during periods when most SARS-CoV-2 infections, at the population-level, are caused by the Delta variant versus periods when Omicron variant is responsible for most COVID-19 cases 2. To assess frequency of previous vaccination in hospitalised patients and severity of disease in vaccinated versus unvaccinated individuals before versus after the spread of Omicron variant Secondary objectives: 1. To characterise the clinical profile (demographics and symptoms at admission) of hospitalised patients during periods when Delta is dominant versus when Omicron is the dominant variant

2. To estimate prevalence of comorbidities in hospitalized patients before versus after the spread of Omicron variant

Proposed Target Population

All COVID-19 hospitalised cases admitted from 01 November 2021 to February 2022. For ISARIC partner sites that also contributed data during recent months before Omicron variant emergence, data from this period will also be analysed. For this analysis, that will use community-level variant data, individual-level data on SARS-CoV-2 variant genotyping are not required.

Clinical Questions/Descriptive Analyses

1. *Will there be differences in disease severity (death and invasive mechanical ventilation) during periods when Delta is the main infecting variant in the community versus periods when Omicron is the dominant variant?*
2. *Will there be differences in vaccination status of hospitalised patients before versus after the spread of Omicron variant? And will vaccine effectiveness against in-hospital disease severity be different in these two periods?*
3. *Will the spread of Omicron variant lead to changes in presenting symptoms and patient characteristics (demographics and comorbidities) for hospitalised COVID-19 cases?*

Planned Statistical Analyses, Methodology and Representation

General approach

Analyses that compare clinical presentation and outcomes of hospitalised patients with Omicron versus Delta variants are urgently needed to inform policy and guide response. Whilst clinical data linked to individual-level information on infecting variant would allow direct comparison of infections with different variants, in many settings infrastructure might not yet be available that allow systematic genotyping of samples or mutation-specific

PCR-based approaches . As an alternative or complementary approach, here we propose analyses that compare characteristics and outcomes of patients hospitalised during time windows when different SARS-CoV-2 variants are dominant. Note that, as mentioned in the Introduction section, whilst the analytical approach described here relates primarily to describing clinical presentation and outcomes before and after the spread of the Omicron variant, as part of this SAP, we will also perform these analyses to the study of the emergence of other SARS-CoV-2 variants. As a subanalysis, we will also perform similar comparisons (e.g. relating clinical outcome) for patients admitted to intensive care unit.

Before describing analytic approaches relevant to each of the questions listed above, in this section, we discuss aspects of this work that are relevant to all questions: (1) definition of time periods when different variants are dominant; (2) considerations on population-level data on SARS-CoV-2 variant; (3) preferred strategy for hospital data acquisition during the analysis period (November 2021 – February 2022).

Definition of time periods when different variants are dominant

Whilst weekly or bi-weekly data on clinical outcomes will be combined with population-level variant-specific frequency data to graphically assess progressive changes linked to Omicron variant spread, a key component of analyses described in this document is the use of time windows to categorise infections as being likely caused by Delta versus Omicron variants. Precise dates used to define time windows will likely be different in different countries, and possibly in different regions within countries, if Omicron variant spreads asynchronously at the regional level.

Although it is possible that the Omicron variant will become the dominant variant in many settings, other epidemiological outcomes should be considered in the planning of this analysis, including plateauing of the relative frequency of Omicron, versus Delta, variant at intermediate levels. Due to current uncertainty in the future spread of Omicron variant, we will assess population-level data on relative frequency of Omicron variant at the time of analysis. The following approaches will be considered:

- Countries will be grouped based on population-level frequency of Omicron variant at the end of the analysis period (February 2022): for example, if appropriate, given magnitude of future spread of Omicron variant, countries or subnational regions could be categorised as having < 30%, 30 – 60%, 60 – 90% and > 90% of community infections due to Omicron variant
- Where increase in relative frequency of Omicron variant will take place within a short time period (weeks), the time period variable will be binary (period with primarily Delta variant infections and period with primarily Omicron variant infections); where slower increase in relative frequency of Omicron variant is observed, the time period variable might include more than two categories.

In addition to data that will be prospectively collected from November 2021, we plan to include data collected in October 2021 to inform baseline characteristics before Omicron variant emergence. Avoiding use of data collected before this period will enhance comparability with prospective data, including in terms of previous exposure to infection and vaccination campaigns.

Considerations on population-level data on SARS-CoV-2 variant

Since our goal in this analysis is to generate insights on the clinical presentation of hospitalized COVID-19 patients, rather than on the entire population of infected individuals, which would include asymptomatic and mild infections, when identifying data sources on the population-level frequencies of variants, we will prioritise data from studies or surveillance systems that used samples from hospitalised patients. The rationale for this is that differences in disease progression (from infection to severe disease requiring hospitalisation) between variants, either due to inherent pathogenic differences or to variant-specific vaccine effectiveness, would mean that community-level data on variant distribution based on mild cases might not reflect variant distribution in our analysis population. If population-level data on relative frequencies of variants are only available for milder clinical cases, these data will be used. Of note, in the latter scenario, in defining

the time periods when different SARS-CoV-2 variants dominate, we will use information on the estimated time from infection to hospitalisation in other epidemiological studies.

Preferred strategy for hospital data acquisition during the analysis period

To maximise use of data collected during this period, we encourage ISARIC partners to record information on a random or systematic sample of admitted patients, selected independently of their outcomes, vaccination status, infecting variant or comorbidity. Additional information on recruitment strategies is described in Appendix A.

Statistical approaches to answer research questions

Characterising disease severity in hospitalized patients during periods when Delta versus periods when Omicron is the dominating variant

There is epidemiological evidence that disease severity can vary in patients infected with different SARS-CoV-2 variants.(2) Currently only limited data are available on the clinical outcomes of patients infected with Omicron variant. In this subsection, we describe analyses that will be performed to assess relative severity of COVID-19 hospitalised cases during time periods when Delta is the most frequent circulating variant versus when most infections are caused by the Omicron variant.

Outcomes: The primary outcome in this analysis is a composite outcome that consists of invasive mechanical ventilation or death. Secondary outcomes include death and admission to intensive/high-dependency care unit. Data from hospitals where invasive mechanical ventilation or intensive care unit are not available will only be included in the analysis on death outcome. 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.

Statistical approach: For each country, or subnational region if appropriate, we will generate time series plots of in-hospital case fatality rate and of composite outcome (death and invasive mechanical ventilation) count by week or 2-week calendar time period,

depending on the number of patients studied. For this, only data on the first 14 (28, in secondary analysis) days after admission will be considered. Population (national or subnational) level data on relative frequencies of variants will also be presented in these plots.

Survival curves, up to 14 (or 28) days after admission, of composite outcome and death will be plotted, using the Kaplan-Meier method, for hospitalized patients admitted in the different time periods. Cox proportional hazards models will be fitted with time period as the explanatory variable of interest; patients who are lost to follow-up (e.g. transferred to another facility) will be censored at the time last known to be alive and patients who are discharged alive will be censored at 14 (or 28) days. We will initially fit an unadjusted model, stratified by country, to assess changes in severity before and after the spread of Omicron (i.e. during period when Delta variant is dominant versus when Omicron variant is dominant). A model will also be fitted that will adjust for age, sex, vaccination status, and number of comorbidities, stratified by country. The proportional hazards assumption will be checked. Additionally, we will compare the rates of death in each site using group-level explanatory variables.

Vaccination status of hospitalised patients and disease severity in vaccinated and unvaccinated individuals before and after Omicron variant spread

An important question is whether vaccines are equally effective against Omicron and Delta variants. Whilst several types of study design can be used to assess vaccine effectiveness when individual-level data on infecting variant are available, in this document we describe analysis that do not use individual-level variant data. Since the emergence of Omicron variant has prompted changes in vaccination policies in many countries, analysis described in this subsection might be confounded by recent increase in vaccination coverage and administration of booster doses, among others.

Comparison: We will compare the frequency of previous vaccination in hospitalized patients during the period when Delta is the most frequent variant versus when the

Omicron variant dominates. Furthermore, we will assess the association between previous vaccination and in-hospital outcome during these different periods.

Statistical approach: Plots will be generated that present the frequency of previous vaccination in hospitalised patients by week or 2-week calendar time. If population-level data on vaccine coverage are available, these will be presented alongside clinical data. Logistic regression will be used to estimate the associations of vaccination (and vaccination regimen) with time window, as a proxy for likely infecting variant, adjusting for age, sex, comorbidities, ethnic group. Since frequency of previous vaccination in hospitalised patients depends on context-specific factors for which direct data might not be available (or with which its relationship might be complex), including recent and earlier vaccination coverage, analyses for this outcome will be presented at the country level, rather than pooled across different countries.

Survival analyses will also be performed, using models similar to those described in the previous subsection, to assess the association of vaccination with severe outcomes in hospitalized patients during time periods when Delta versus Omicron variants cause most infections. Analyses will be performed for different time periods separately, and will also include a multivariable model to test for multiplicative interaction.(3) To account for possible waning of vaccine efficacy, we will perform secondary analyses that stratify the exposure variable of vaccination status by time since last vaccine dose.

Symptom profile and concomitant medical conditions in hospitalised patients infected before and after the spread of Omicron variant

We will also assess temporal changes in the frequencies of symptoms and comorbidities in hospitalised COVID-19 patients during periods when different variants are common.

Outcomes: Patient characteristics (age and sex), frequent symptoms and comorbidities will be compared between COVID-19 patients hospitalised during different periods in each country.

Statistical approach: Comparative plots will be generated with frequencies of most common symptoms and comorbidities for each country and by time window. Frequent symptoms (fever, cough, shortness of breath, fatigue) and comorbidities (hypertension, diabetes, obesity, smoking) will be compared between time periods with different 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.

In addition to these approaches, we will assess changes in relative frequencies of hospitalised patients from different age groups, applying methodology used earlier in the pandemic,(4) and described in Goldstein et al 2017.(5) Briefly, we will compare proportions of hospitalized cases from each age group during time periods when Delta variant is the most frequent versus time periods when Omicron variant is the most frequent variant. Comparisons between age groups can be performed using the ratio of these relative quantities.

Handling of Missing Data

Missingness in the data will be assessed for all variables, by country and calendar month. This will enable the identification of variables that lack sufficient data 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

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2. Patone M, Thomas K, Hatch R, Tan PS, Coupland C, Liao W, et al. Mortality and critical care unit admission associated with the SARS-CoV-2 lineage B.1.1.7 in England: an observational cohort study. The Lancet Infectious Diseases. 2021 Nov 1;21(11):1518–28.

3. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. International Journal of Epidemiology. 2012 Apr 1;41(2):514–20.

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Appendix A.

Guide to participate in Characterising SARS-CoV-2 Omicron vs Delta variant in terms of vaccination status, clinical presentation and outcomes

SELECTION of PATIENTS for DATA COLLECTION

This analysis will include all individuals with confirmed SARS-CoV2 infection.

A robust analysis requires methodical selection of patients for data collection. We understand that each site has its own requirements, abilities, and limitations to data collection, therefore we have designed a flexible way to select the approach that's right for your site.

Please choose from the following approaches to patient selection.

Type of sampling	Explanation
Census	Collect data on all SARS-CoV-2 patients who present to your hospital
Sequential/systematic sampling	Choosing patients based on their time of presentation. E.g., every 3rd patient who presents to the hospital, or all patients who present on even calendar days (2nd, 4th, 6th)
Simple random sampling	Use a tool to randomly determine if each patient is included. E.g., to include 50% of patients, you can toss a coin, or use an excel sheet (like the one you can download at this link) or an online tool to generate a random list of Yes/No variables in the desired proportion and apply them sequentially as patients present (note: this should be done so that no one knows the next variable)
All ICU only	Collect data on all SARS-CoV-2 patients admitted to ICU
All omicron variant only	Collect data on all SARS-CoV-2 patients with confirmed omicron variant

Email ncov@isaric.org to inform ISARIC of which sampling method is used at your site and anytime the method changes.

This analysis will not include data from sites that select patients without any criteria or method. The benefits and limitations of each of these approaches is outlined in APPENDIX A – Strategies for patient selection.

SYSTEMS and KEY VARIABLES for DATA COLLECTION

Data will be collected on the ISARIC COVID-19 CORE and RAPID case report forms, available on the ISARIC REDCap system. To access REDCap, please email ncov@isaric.org.

Data required for this analysis are highlighted in the versions of the CRFs linked above and include those on MODULE 1 and MODULE 3 or each form. Laboratory confirmation of SARS-CoV2 virus and variant are the only laboratory values required for this analysis (no other labs).

STATISTICAL ANALYSIS PLAN

You can view and comment on the statistical analysis plan here: https://docs.google.com/document/d/1605hG37ZVBhYJFRImF3JfVzPmbn7WmdQ/edit?usp=sharing&ouid=105842004335982851322&rtpof=true&sd=true

APPENDIX A.1: STRATEGIES FOR PATIENT SELECTION

Summary of strategies and advantages for sites.

Strategy	Clinical characterization at hospital level	Risk factors for severity at hospital level	Relative vaccine effectiveness estimates comparing variant X vs Y	Characterization of vaccine breakthroughs comparing variants X vs Y	Local/national surveillance
Convenience/no method	No	No	No	No	No
All ICU only	No	No	No	Yes, limited	Yes, limited
All omicron only	No[1]	No[1]	No	No	Yes, limited
Non-biased[2]	Yes	Yes	Yes	Yes	Yes

[1]Yes, if variant X is the only one circulating in that area.

[2]Simple random sample (i.e., all patients have an equal probability of selection), sequential / systematic sampling (every other day, every fifth patient), or census (i.e., all patients).

Strategies for patient recruitment and their advantages for sites and pooled analyses.

Recruitment strategy	Procedure	Possible analytics for the site	Possible pooled analytics (partner analysis)
Convenience			
No specific pattern	Patients are enrolled based on time availability or ad-hoc.	Description of patients in the database without reliable information on hospitalized patients at the site level.	Limited analytical capacity due to lack of knowledge on the representativeness of study patients regarding hospitalized patients. With a throughout explanation of the selection process, these data

			could be included in specific analyses.
Exclusion criteria			
ICU only patients	All ICU patients are included.	Clinical characterization of ICU patients to inform hospitals and governments on characteristics of ICU patients. Risk factor analysis for outcomes at ICU level.	Clinical characterization of ICU patients and risk factor analysis for outcomes at ICU level.
Variant specific patient inclusion	Only variant X patients are included.	Clinical characterization of variant X patients.	Clinical characterization of variant X patients.
Random sampling*			
Sequential sampling	A sequential process is used to select patients. Examples: every fifth patient is entered into the database. Patient data are collected on Monday, Wednesday, Friday	Clinical characterization, risk factor analysis for hospital outcomes. Depending on the number of hospitals and the hospital catchment area, these data could inform national surveillance systems.	Clinical characterization, risk factor analysis for hospital outcomes at an international level. Partners can benefit from a worldwide dataset with high power for statistical analysis.
Random sampling	A given proportion of patients are randomly selected to be included in the database.	Clinical characterization, risk factor analysis for hospital outcomes.	Clinical characterization, risk factor analysis for hospital outcomes at an international level. Partners can benefit from a

	For example, if 50% of patients are included, a coin can be flipped to determine if the patient should be entered into the dataset. More sophisticated systems exist.	Depending on the number of hospitals and the hospital catchment area, these data could inform national surveillance systems.	worldwide dataset with high power for statistical analysis.
Census			
Census	All patients that arrive at the hospital are recruited	Clinical characterization, risk factor analysis for hospital outcomes. Depending on the number of hospitals and the hospital catchment area, these data could inform national surveillance systems.	Clinical characterization, risk factor analysis for hospital outcomes at an international level. Partners can benefit from a worldwide dataset with high power for statistical analysis.

*For this category, the sampling strategies can be replicated under different population subsets. For example, a random sample of variant X and variant Y patients are selected. This would allow for comparative coverage of vaccine or concomitant conditions between variants.