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Title

WHO O2CoV2: Oxygen requirements and respiratory support in patients with COVID-19 in low- and middle-income countries – protocol for a multi-country, prospective, observational cohort study

Authors

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Keywords: Oxygen; emergency care; critical care; Low- and- middle-income countries (LMICs); severe acute respiratory illness (SARI); COVID-19

Abstract (Word count = 296).

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as the cause of the disease officially named COVID-19, primarily a respiratory illness. COVID-19 was characterized as a pandemic on 11 March 2020. It has been estimated that approximately 20% of people with COVID-19 require oxygen therapy. Oxygen has been listed on the WHO Essential Medicines List and Essential Medicines List for children for almost two decades. The COVID-19 pandemic has highlighted, more than ever, the acute need for scale-up of oxygen therapy. Detailed data on the use of oxygen therapy in LMICs at the patient and facility level are needed to target interventions better globally.

Methods and analysis

We aim to include better describe the requirements and use of oxygen at the facility and patient level of approximately 4,500 patients with COVID-19 in 30 countries. Our objectives are specifically to characterize type and duration of different modalities of oxygen therapy delivered to patients; describe demographics and outcomes of hospitalized patients with COVID-19; and describe facility level oxygen production and support. Primary analyses will be descriptive in nature. Respiratory support transitions will be described in Sankey plots and Kaplan-Meier models will be used to estimate probability of each transition. A multi-state model will be used to study the course of hospital stay of the study population, evaluating transitions of escalating respiratory support transitions to the absorbing states.

Ethics and dissemination

World Health Organization AdHoc Covid-19 Research Ethics Review Committee has approved this global protocol. When this protocol is adopted at specific country sites, national ERCs may make require adjustments in accordance with their respective national research ethics guidelines. Dissemination of this protocol and global findings will be open access through peer-reviewed scientific journals, study website, press and online media.

Registration details: Clinicaltrials.gov number NCT04918875.

Article Summary

Strengths and limitations of this study:

- This study is the first global description of oxygen use and respiratory support approaches for patients with COVID-19 collated from over 20 low-and-middle income countries (LMICs).
- The study will describe oxygen supply systems and oxygen production capacities in over 50 hospitals in LMICs and link this facility-level information to patient outcomes through multistate model.
- The outcomes of this study will be used to inform future respiratory support research for COVID-19 and other conditions that require oxygen.
- The study offers a unique opportunity to build capacity in and between countries for conducting clinical research.
- Though variability in devices across countries limit precise calculations of oxygen consumption, this study is the first to attempt to estimate this on a global scale.

Word count (excluding title page, abstract, references, acknowledgements): 3022

Introduction:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as the cause of the respiratory disease officially named COVID-19. COVID-19 was declared a Public Health Emergency of International Concern on 30 January 2020 and characterized as a pandemic in March 2020[1].

Since January 2020, it has been estimated that approximately 20% of patients with COVID-19 develop hypoxia and require oxygen supportive therapy. Oxygen is an essential medicine and has been listed as such on the World Health Organization (WHO) Essential Medicines List and Essential Medicines List for children for almost two decades[2,3]. However, in many low and lower-middle income countries, there is inadequate production, supply and use of medical oxygen.

COVID-19 pandemic has highlighted, more than ever, the acute need for scale up of oxygen supply systems. WHO has published a biomedical inventory tool to quantify facility-level infrastructure and resources for the delivery of oxygen[4] and launched a global oxygen access scale up initiative[5]. However, data on the status of oxygen systems, their use and implications of oxygen therapy on patients in low- and middle-income countries remains lacking.

In February 2020, the WHO Research and Development Blueprint for COVID-19 identified key research areas needed for understanding this new disease[6]. One priority area was the types of respiratory support required by patients. To take this forward, the WHO COVID-19 Clinical Characterization and Management research group created a subgroup, the WHO Respiratory Support Research Group, to develop research protocols concerning respiratory support practices and oxygen requirements for the clinical management of COVID-19. Understanding of current practice and available resources in potential sites globally is required.

At the patient level, existing studies collect data on oxygen mode of delivery, but do not characterize the type, quantity and duration of each modality's use and compare transitions across devices[7]. At the facility level, existing studies describe overall hospital surge capacity but do not give an overview of capacities at the country, regional or global level[8]. Given the call for more sustained global efforts to better target interventions for oxygen systems in LMICs, such as through the Lancet Commission on medical oxygen security and others, a more succinct exploration of oxygen use in LMICs is required.[9]

The objectives of O2CoV2 are to: 1) characterize the type and duration of different modalities of oxygen therapy and respiratory support consumed by patients with severe and critical COVID-19 2) describe demographics and outcomes of hospitalized patients with COVID-19 and 3) describe facility level oxygen production capacity. All objectives are aimed to further inform a future WHO-supported platform trial of respiratory support strategies.

Methods and analysis

STROBE cohort reporting guidelines were used. [10]

Study design

The master protocol serves to describe an observational cohort study from June 2021 through March 2023 that will be implemented in 30 countries representing four low-and-middle income countries (LMICs) from each of the six WHO regions, and targeting up to 4 hospitals per country. LMICs will be defined as per 2021 World Bank criteria and codes "UMC", "LMC" and "LIC"[11]:

Code	Description
HIC	World Bank high-income economies (GNI per capita of USD 12,696 or more in 2020)
UMC	World Bank upper middle-income economies (GNI per capita of USD 4,096 - 12,695 in 2020)
LMC	World Bank lower middle-income economies (GNI per capita of USD 1,046 - 4,095 in 2020)
LIC	World Bank low-income economies (GNI per capita of USD 1,045 or less in 2020)

Study site selection

To recruit interest in participation, WHO put out a global call for expressions of interest global clinical research networks, social media, WHO website and WHO internal communications through headquarters, regional offices, and country offices. An information sheet about the study was provided for public use on WHO study webiste[12]. Expressions of interest were requested to include information about previous experience with WHO and clinical research, research staff, and COVID-19 burden. See Annex 1.

Site selection was conducted by the WHO O2CoV2 International Study Steering Committee (ISSC)[13]. Study sites were limited to health facilities where patients with severe and critical COVID-19 are cared for, including hospitals and temporary COVID-19 treatment centres. The following considerations were considered when selecting sites: WHO region of country; income status of the country (per World Bank criteria); previous history of conducting research before; having dedicated research staff; having identified a paired site. The African and American regions underwent sub-regional division prior to site randomization to have at least 1 country within each subregion of the continent. Finally, EOIs were randomized among regions.

Study population and enrolment

Participant eligibility criteria:

1. Age greater than 12 years.
2. Suspected SARS-CoV-2 infection as determined by treating clinical provider or confirmed SARS-CoV-2 infection confirmed virologically in the laboratory by reverse transcription polymerase chain reaction (RT-PCR) via nasopharyngeal or oropharyngeal sample or by SARS-CoV-2 Ag-RDTs that meet the minimum performance requirements of ≥ 80% sensitivity and ≥ 97% specificity compared with a nucleic acid amplification test (NAAT) reference assay.
3. Admitted to health care facility within 24 hours.
4. Receiving supplemental oxygen or showing clinical evidence of need for supplemental respiratory support as reflected in a respiratory rate ≥ 30 breaths per minute or an $SpO_2 \leq 90\%$, $SpO_2 < 94\%$ if any emergency signs are present.
5. Committed to full supportive care.

Study procedures

Screening

Patients will be screened for inclusion over a maximum of 30 days or until the site level sample size is met, whichever comes sooner. During the recruitment window, patients will be screened for inclusion in the study 24 hours per day, 7 days per week, as they enter the facility for acute care in an emergency unit or area of the hospital that functions like an emergency unit. An information note (see Annex 2) about the study will be posted at all potential areas where screening will occur; thus, informing potential patients that they are being screened and may be enrolled in study. A daily screening log (Annex 3) will be maintained to capture daily numbers of patients screened and those that are enrolled.

Observational period

Patients who meet the inclusion criteria for enrolment will be visited once a day for up to 7 days for daily clinical data collection, or until outcome occurs, whichever happens first. Designated study data collector will review the patient bedside chart and observe the patient and surroundings to collect relevant data.

Data collection will occur daily using an electronic case report form (eCRF) and data entry platform (REDCap) on a WHO-provided tablet computer. See Annex 3 for all CRFs.

Follow-up phase

In cases where the patient remains in hospital more than 7 days, then the data collector will visit the patient each additional day until the patient hospital outcome up to 30 days maximum, to assess only vital status, and, at that time, complete the outcome form.

Link to the platform trial

Through the conduct of the cohort study an established dialogue with site investigators will have been established. For the platform trial, expressions of interest to participate in the full trial will be sought and a final decision will be based on site interest and site capacity as determined in this cohort study.

Statistical analysis

All analyses will be conducted in R (R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria 2020, https://www.R-project.org).

Missing data

For each analysis, the denominator will represent data that are available. To impute missing data, random forest imputation will be considered.

Sample size

To maximise statistical power, we aim to recruit as many participants as possible. The larger the sample, the greater the precision and generalization of the results, and thus for descriptive analyses we aim for at least 125 patients per hospital, a maximum total of 4,500 patients. For inferential analyses, sample size estimates suggest a minimum of 1,380 patients to attain 95% statistical power to achieve hypotheses discussed with the ISSC.

Selection bias

To minimize selection bias, the following are introduced:

a) systematic and randomized site selection procedure (described above);
b) specific objective criteria for participant study eligibility (described above);
c) waiver of informed consent (see ethical considerations).

Outcomes

To characterize the type and duration of different modalities of oxygen therapy and respiratory support consumed by patients with severe and critical COVID-19, the following outcomes will be reported:

- Baseline characteristics of patients;
- Hospital outcomes of patients;
- Total of patients receiving respiratory support daily and proportion of patients receiving various delivery devices: nasal cannula, face mask, Venturi, non-rebreather, HFNC, CPAP, bilevel positive airway pressure (BiPAP), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV).
- Proportion of patients progressing to IMV.
- Description of respiratory support over time, with subgroup analysis by disease severity, and associations between facility type or patient characteristics.
- Quantification of total oxygen requirements will be estimated by daily oxygen use as from data collected on flow rates, fraction of inspired oxygen (FiO_2), positive end expiratory pressure (PEEP).

Sankey plots for patient trajectories will be used to describe the proportion and duration of each type of respiratory support intervention overall and in subgroup of disease severity. Multistate models will be used to quantify duration of stay in, and transition probabilities across, modes of respiratory support distinguishing absence, nasal or facial, HFNC, IMV, with death and discharge from hospital as absorbing states. Multivariable models will be used to predict transition to IMV or death based on patient and facility characteristics at the time of hospital admission. The following characteristics will be considered: age, chronic conditions, need for oxygen on day of transition and facility.

The amount of oxygen used for each patient will be computed using the following formulas:

- For nasal cannula, face mask and non-rebreather mask, FiO2 is assumed to be 1.0 and flow rates are adjustable in litres per minute (LPM). Litres per day consumption of oxygen = device flow rate L/minute x 60 minutes/hr x 24 hr/day.
- For HFNC FiO2 is adjustable (defaulted to 1.0) and flow rate is adjustable in LPM. Litres per day consumption of oxygen = device flow rate L/minute x 60 minutes/hr x 24 hr/day; flow rate in LPM = device flow rate x (FiO2 - 0.21)/0.79.
- For ventilator, CPAP, BiPAP/non-invasive positive pressure ventilation (NIPPV), FiO2 is adjustable (defaulted to 1.0) and flow rate is adjustable in LPM and dependent on multiple factors. Litre per day consumption of oxygen = device oxygen consumption rate L/minute x 60 minutes/hr x 24 hr/day. Device oxygen consumption rate in LPM = (minute ventilation + (bias flow x RR x expiratory time/60) + leak) x (FiO2 - 0.21)/0.79.

To describe oxygen source, distribution and biomedical equipment at facility level and estimated oxygen capacity at the facility level, descriptive statistics for relevant variables and quantification of total oxygen supply at each facility will be determined.

Full statistical analysis plan available in Annex 4.

Study administration

Data collection and management

Standardized case record forms (CRFs) are available and include:

- screening form;
- case identification and demographics form;
- initial case information form;
- daily follow-up form (to be filled in day 2–7 or until outcome if sooner);
- daily vital status form (to be filled in day 8-30 or until outcome if sooner);
- case outcome form; and
- facility form.

WHO will support data management and access to data entry platform REDCap, that will be stored in a secure WHO server housed in Geneva. The WHO team, within the capacity of research strengthening, will support the development of local data platforms. Implementing partners can opt to manage data on site or through the central WHO repository, subject to local circumstances.

Each participant will be linked to an anonymous study ID within the REDCap database. A locally designated data manager will be sent a password-protected copy of the online database (anonymized and without any patient identifiers) for data analysis.

For local data collection which may occur on paper, all data must be stored in a password-protected database or kept in a locked storage in accordance with national regulations. An identification log will be used, and this log will be stored in a secure, locked facility within the study country. The location of and responsibility for local database(s) will be determined on a case-to-case basis and dependent on national regulations.

All essential study documents, including CRFs, will be electronically archived and retained at WHO for 3 years or for the duration required by the national laws and regulations at local research centres. This is to enable completion of the study, to conduct and complete data curation processes, and to finalize the publication and archival process. The sharing of anonymized data will be done using standard WHO data sharing agreements (see Annex 5) with each study site.

Study personnel at sites: roles and responsibilities

- PIs at all sites will be responsible for the submission and approval process of protocols to institutions.
- Study investigator team will be responsible for all aspects of protocol implementation, including screening, enrolment, daily data collection over 7 days, and follow up until hospital discharge, and facility on-time assessment.
- Clinicians and hospital staff at sites will be minimally impacted as separate data collecting personnel should be hired to collect information and not directly interact in patient care.
- If the above is not feasible, the potential source of bias will be acknowledged in the report. Note: excluding such sites would likely result in exclusion of sites with the most limited resources, which is the focus of the study and the trial.

WHO will serve as central coordinator of all sites and staff will support implementation of the study in all sites, including good clinical practice training.

Patient and public involvement statement:

As part of WHO usual practice, public and patients were engaged in the development of this protocol via the WHO Clinical Characterization and Management working group which led to the voluntary formation of the Respiratory Support Research Working Group, who edited this protocol.

Ethics and dissemination

Ethics approval: World Health Organization AdHoc Covid-19 Research Ethics Review Committee (CERC.0040)

Ethics

WHO ERC has determined that this master protocol meets the Council for International Organizations of Medical Sciences (CIOMS) criteria justifying a waiver of consent. When this protocol is adopted at specific country sites, national ERCs may make a different determination regarding consent in accordance with their respective national research ethics guidelines, for example, requiring modified consent or full individual consent as appropriate.

A wavier of consent is suggested, whereupon each study site can then consider consent exemptions according to national ethical review boards (ERBs). We kindly request this for the following reasons:

- **One, the research would not be feasible or practicable to carry out if informed consent were required.** Our objective is to understand current practice, including capacity and limitations. To do this reliably, we need to have rudimentary data on the entire population at risk, and not simply those who are able to provide consent. A biased estimate, such as would result from the requirement that data only be collected from patients who have provided consent, will provide an inaccurate picture of capacity, resources and outcomes at sites which in turn would not only compromise the data, but also pose potential risk to patients recruited to the trial. As well, by virtue of their illness, patients are often unable to provide first-party consent, and third-party consent is challenging because of restrictions on visiting.
- **Two, this research has important social value.** Understanding the nature of the challenge in resource-limited settings is a prerequisite to developing approaches to address these. Respiratory insufficiency is the dominant cause of death for patients with COVID-19, and so understanding its management has compelling social value.
- **Three, this research poses no more than minimal risks to participants.** We seek waiver of consent for data collection only; no specific study interventions will be undertaken. Further we will record only basic physiological data and location in the hospital, and not personal health information that might be identifying or stigmatizing. Finally, all data are anonymized, and linked to patient identity only through a linkage log that will be maintained **securely at study sites.**
- **Four, ERCs at national level will have full authority to request waiver of consent as per national protocols.**
- **Five, an information note will be posted in all areas where potential screening may occur.** Annex 2 is an information note that can be posted in all areas where potential screening may occur and includes simple language that can be translated into local languages for local ERB approval.

It is of the utmost importance that participant confidentiality be maintained throughout the study. This study will use standard methods in order to protect the confidentiality of participants. All study participants will be assigned a unique, pre-defined study identification number by the investigation team for the labelling of questionnaires for attribution of data to an individual subject and study site.

The study will remove all identifiers from any data collected for this study at the individual and study site levels. No names or other directly identifying information, including addresses or medical information, will be entered in the regional or global databases. Study identification numbers will be linked to investigator records stored separately in a secured, locked cabinet and making it possible to identify the case in order to correct missing or erroneous data, in accordance with institutional requirements.

Outputs and dissemination

Each site will be invited to share their anonymized data for pooled analysis and will also be able to publish their own data independently. To protect patient identity, any publications or presentations relating to the study will use only aggregate summary data. Further, after obtaining agreement from each study site, the use of the master protocol and harmonized collection of data will allow for pooled analyses, which in turn will contribute to rapid knowledge generation and strengthen the power of the data analysis to make recommendations. Reporting forms of site-specific results is up to individual investigators and should follow Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies and ideally be reported in such a way to allow for comparison of data across different study sites.

At the global level, dissemination will be done in the standard ways to inform clinical management and WHO guideline development work. Findings from the global pooled analysis will be presented in reports and peer-reviewed publications.

Authorship will be determined using accepted international approaches, according to International Committee of Medical Journal Editors recommendations (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html), commensurate to contributions made.

Author Contributions

PR wrote the protocol with input from JD, SDR, chairs of the WHO COVID-19 clinical characterization management group (SR and JM), key contributors of the respiratory support research group (DA, SC), and chairs of the WHO International Study Steering Committee (YA, WS, PC). All other authors reviewed the document and made editorial suggestions.

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*WHO Respiratory Support Research Working Group: Neill Adhikari, Diptesh Aryal, Tim Baker, Devasahayam J Christopher, Rob Fowler, Martha Gartley, Ewan Goligher, Rashan Haniffa, Devachandran Jayakumar, Richard H Kallet, Richard Kojan, Arthur Kwizera, Jie Li, Armand Mekontso-Dessap, Christian Paletta, Ingrid Lara Rendon, Elisabeth Riviello, Jorge Salluh, Jonathan A C Sterne, Bruno Martins Tomazini, Bharath Kumar Tirupakuzhi Vijayaraghavan, Fernando Zampieri.

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Dina Pfeifer, Cinzia De Brito Procopio, Ingrid Lara Rendon, Ludovic Reveiz, Elisabeth Riviello, Matthieu Rolland, Amadou Seck, Elizabeth Stanway, Julie Viry, Pushpa Wijesinghe.

Data statement

All study forms available in Annex 3.

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Competing interests statement

None declared.

Trial registration number Clinicaltrials.gov number NCT04918875.

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Oxygen requirements and approaches to respiratory support in patients with COVID-19 in low- and middle-income countries: a WHO study

Annexes

Contents

Annex 1. Expression of interest

WHO Respiratory support research in low- and middle-income countries: Expression of interest (to be filled by interested facilities)

The WHO Respiratory Support Research Working Group, part of the Clinical Characterization and Management of COVID-19, has developed protocols for two studies designed to address the optimal respiratory support of patients with severe COVID-19 in LMICs:

1. An observational (cohort) study to understand current practice, limitations, experience and outcomes.

2. A randomized clinical trial to test the ability of a variety of approaches to reduce mortality and the need for intubation and mechanical ventilation.

We are looking for sites who can recruit patients to both the cohort study and the trial. If you and your site are interested in being involved, please provide us with the following information:

Name: _____
Email address: _____
Site(s): _____
City/Region: _____
Country: _____

Have you/your site previously participated in clinical research?
Observational studies: Yes ____ No ____
If yes, approximate number: 1–2 ____ 3–5 ____. 6 or more ____
If yes, were any of the studies you participated in linked to WHO?
Yes ____ No ____
If yes which ones?

Clinical trials: Yes ____ No ____
If yes, approximate number: 1–2 ____ 3–5 ____ 6 or more ____
If yes, were any of the studies you participated in linked to WHO?
Yes ____ No ____
If yes which ones?

Who collects data or recruits patients at your site? (check all that apply)
Medical doctors ____
Nurses ____
Trainees ____
Dedicated research staff ____
Other ____

On average, how many patients with COVID-19 have you admitted monthly in the past 3 months? ____

May we contact you to discuss the opportunity further?
Yes ____ No ____

Any additional comments? _____
Thanks for your input.

Annex 2. Site information sheet for public posting visibly in sites

WHO Respiratory Support Research Working Group Observational Study
Information sheet for public posting at site

The World Health Organization (WHO) is conducting an observational research study of low- and middle-income country (LMIC) sites to examine baseline practices and resources for oxygen and respiratory care for patients with COVID-19.

This study will help the global community understand the current practices around oxygen use and help support a future study about advanced respiratory support interventions.

This site is enrolled in this study.

Patients who meet eligibility criteria will automatically be enrolled in the study. Eligibility criteria are:

1. Have suspected or confirmed COVID-19.
2. 12 years age or older.
3. Determined by treating clinician to require admission to facility.
4. Determined by treating clinician to require oxygen or has fast respiratory rate or low oxygen saturation.

Daily information about patients will be collected for the first 7 days of hospitalization and once again at hospital discharge. If you are discharged before 7 days, then it will be shorter. If you are hospitalized more than 7 days then you will be visited once a day until your discharge.

The types of information collected will be vital signs and details about the type of oxygen support you may be treated with such as how much oxygen are you being treated with, what kind of face mask or pressure mask is being used to give you the oxygen.

World Health Organization

Annex 3. Case report form

Confidential

A_Case screening

Screening ID: _____

Date and time screening is initiated _____

Data collector username: _____

Name of data access group/facility: _____

Identifier of data access group/facility: _____

World Health Organization

WHO O2CoV2 Screening Form

1a. How old is the patient? _____
(If patient is under 1 year of age, enter age as "999")

This patient is not eligible for this study. Please thank them for their time and proceed to the next patient for screening by:

Mark this form status as "Complete" Select "Save and Exit Form" Select "Create New Record"

2a. Does the patient have suspected or confirmed SARS-CoV-2 infection, as determined by treating clinical provider?
- ◯ Yes
- ◯ No

This patient is not eligible for this study. Please thank them for their time and proceed to the next patient for screening by:

Mark this form status as "Complete" Select "Save and Exit Form" Select "Create New Record"

World Health Organization

Confidential

3a. Is this patient being admitted to the health care facility or was the patient admitted to the health care facility in the last 24 hours?	◯ Yes ◯ No (Being admitted is defined as the patient being expected to stay at least overnight.)

This patient is not eligible for this study. Please thank them for their time and proceed to the next patient for screening by:

Mark this form status as "Complete" Select "Save and Exit Form" Select "Create New Record"

4a. Is the patient: Receiving supplemental oxygen OR With a respiratory rate of ≥ 30 breaths per minute OR With a SpO2 ≤ 90% on room air OR With a SpO2 < 94 % and any one of the following emergency signs are present: Obstructed or absent breathing Severe respiratory distress Central cyanosis Shock Coma and/or convulsions	◯ Yes ◯ No

This patient is not eligible for this study. Please thank them for their time and proceed to the next patient for screening by:

Mark this form status as "Complete" Select "Save and Exit Form" Select "Create New Record"

5a. Is the patient committed to full supportive care?	◯ Yes ◯ No (Full supportive care is defined as the patient is amenable to advanced oxygen support, as is able to be provided at the facility.)

This patient is not eligible for this study. Please thank them for their time and proceed to the next patient for screening by:

Mark this form status as "Complete" Select "Save and Exit Form" Select "Create New Record"

This patient is eligible to be enrolled in the study. This patient should now be assigned a linking identifier and proceed to enrolment.

Please enter the patient's linking identifier below then proceed to screening the next patient by:

Mark this form status as "Complete" Select "Save & Exit Form" Select "Create New Record"

6a. Linking identifier:	_____ (Use this field to uniquely identify the patient to the data collector who will continue with enrollment into the study.)

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B_Case Identification Demographics

Enrolment record ID: _____

Data collector username _____

Data access group name: _____

Data access group identifier (numeric) _____

Time of form start: _____
(Tap NOW when form is started.)

1b. Linking identifier: _____
(Use this field to uniquely identify the patient, from the data collector who screened the patient into the study.)

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WHO O2CoV2 Enrolment Form

2b. Is the patient enrolled in the study?
○ Yes
○ No

This patient is not enrolled in this study. Please thank them for their time and proceed to the next patient.

3b. Please include comments or instructions on how to identify the patient for daily follow up here. Please do not write patient name or medical record/chart number. _____

4b. Date of birth: _____
(Write in DD/MM/YYYY format.)

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5b. Age (years):	_____
Age (years) calculated	_____
The date of birth and age provided are not equal. Please check the age and date of birth provided.	
6b. Sex:	◯ Female ◯ Male ◯ Other
7b. Other sex:	_____
8b. Height (centimetres):	_____ (Write in centimetres without unit label.)
9b. Weight (kilograms):	_____ (Write in kilograms without unit label.)
b. BMI	_____
10b. Is the patient pregnant?	◯ Yes ◯ No
11b. Date of last menstrual period:	_____ (Write in DD/MM/YYYY format.)

Patient's Past Medical History

12b. Chronic cardiac disease (not hypertension)	◯ Yes ◯ No
13b. Hypertension	◯ Yes ◯ No
14b. Chronic obstructive pulmonary disease (COPD)	◯ Yes ◯ No
15b. Asthma	◯ Yes ◯ No
16b. Chronic liver disease	◯ Yes ◯ No
17b. Chronic kidney disease (moderate or severe)	◯ Yes ◯ No
18b. Chronic neurological disease	◯ Yes ◯ No

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19b. AIDS or person living with **HIV**	◯ Yes ◯ No
19b. **Is** the patient currently on **ART** (antiretroviral therapy)?	◯ Yes ◯ No
20b. Diabetes mellitus	◯ Yes ◯ No
21b. Current smoking	◯ Yes ◯ No
22b. Tuberculosis (active and/or previous infection)	◯ Yes ◯ No
23b. Asplenia	◯ Yes ◯ No
24b. Cancer (any type, active in the past 6 months)	◯ Yes ◯ No
25b. Cancer (any type, greater than 6 months remission)	◯ Yes ◯ No
26b. Dementia	◯ Yes ◯ No
27b. Other	◯ Yes ◯ No
28b. Other past medical history:	_____

General Comments

29b. Comments	_____
Time of form completion:	_____ (Tap **NOW** when form is completed.)
Time to complete form:	_____

Please mark the form status as "Complete", then select "Show More Save Options", then "Save & Go to Next Form"

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C_Initial case information

Enrolment record ID: _____

Initial case information (facility arrival/emergency unit)

Time of form start: _____
(Tap NOW when form is started.)

1c. Date of arrival to this facility: _____
(Write in DD/MM/YYYY format.)

2c. Time of arrival to this facility: _____

3c. Was this patient referred or transferred from another facility?
◯ Yes
◯ No

4c. Name of facility where patient referred or transferred from: _____

5c. Date of arrival to previous facility: _____
(Write in DD/MM/YYYY format.)

The date entered is not valid, because it is in the future. Please check the information and re-enter the date.

6c. COVID-19 status:
◯ Suspected
◯ Confirmed

7c. Date of most recent COVID-19 positive test: _____
(Write in DD/MM/YYYY format.)

The date entered is not valid, because it is in the future. Please check the information and re-enter the date.

8c. By which method was the patient's SARS-CoV-2 infection confirmed on [date_covid]?
◯ RT-PCR via nasopharyngeal or oropharyngeal sample
◯ SARS-CoV-2 Ag-RDTs that meet the minimum performance requirements of ≥80% sensitivity and ≥97% specificity compared to a NAAT reference assay
◯ Blood
◯ Other method

9c. Other method: _____

10c. Has the patient received a COVID-19 vaccine?
◯ Yes
◯ No
◯ Unknown

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General comments

11c. Comments

Time of form completion:

(Tap NOW when form is completed.)

Please mark the form status as "Complete" then select "Show More Save Options", and select "Save & Go to Next Form" to complete the daily data (Form D1) for this patient.

Time to complete form:

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D1_Daily case information (Day 1-7)

Enrolment record ID: _____

1d. Please select the day of data collection for which you are completing this form.

- ◯ Day 1 (day of enrolment)
- ◯ Day 2
- ◯ Day 3
- ◯ Day 4
- ◯ Day 5
- ◯ Day 6
- ◯ Day 7

Time of form start: _____

(Tap NOW when form is started.)

Daily, from hospital admission to hospital day number 7

2d. Today's date and current time: _____

(Write in DD/MM/YYYY H:M:S format.)

3d. Location of patient:

- ◯ Emergency unit
- ◯ Ward
- ◯ ICU
- ◯ Other

4d. Other location: _____

5d. Day and time of most recent vital signs: _____

This day and time is not valid, because it is in the future. Please check the information and enter the correct day and time.

6d. Mental status (AVPU):

- ◯ Alert
- ◯ Verbal
- ◯ Pain
- ◯ Unresponsive

7d. Systolic blood pressure (mmHg): _____

(Write in mmHg, without unit label. Example) "70")

8d. Oxygen saturation: _____

(Write in %, without % symbol. Example) "70")

9d. Heart rate (beats/minute): _____

(Write in beats/minute, without unit label. Example) "50")

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10d. Patient positioning:	◯ Prone ◯ Sitting (Fowler's) ◯ Semi-Fowler's ◯ Lateral ◯ Lying flat on back
11d. Oxygen therapy modality:	☐ Room air ☐ Nasal cannula ☐ Simple face mask ☐ Venturi mask ☐ Non-rebreather mask ☐ Hi-flow nasal cannula ☐ CPAP ☐ BiPAP ☐ Intubated ☐ Other
12d. Other oxygen therapy modality:	_____
13d. Oxygen source:	◯ Cylinder ◯ Concentrator ◯ Piped/wall oxygen ◯ Other
14d. Other oxygen source:	_____
15d. Select CPAP type:	◯ Bubble ◯ Nasal pillows ◯ Helmet ◯ Full face mask
16d. CPAP pressure setting:	_____ (Write in cm H2O without unit label. Example) "5")
17d. Select BiPAP type:	◯ Nasal pillows ◯ Helmet ◯ Full face mask
18d. IPAP (inspiratory positive airway pressure):	_____ (Write in cm H2O without unit label. example) "5")
19d. EPAP (expiratory positive airway pressure):	_____ (Write in cm H2O without unit label. Example) "5")
20d. Oxygen flow rate (litres/minute):	_____ (Write in litres/minute, without unit label. Example) "50")
21d. Fraction of inspired oxygen (FiO2):	_____ (Write in %, without % symbol. Example) "50" Reminder: FiO2 of room air is 21%)

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22d. Peak airway pressure (in cm H2O):	_____ (Write in cm H2O without unit label. Example) "50")
23d. Positive end expiratory pressure (in cm H2O):	_____ (Write in cm H2O without unit label. Example) "5")
24d. Tidal volume (in mL):	_____ (Write in mL without unit label. Example) "500")
25d. What is the ventilator mode?	◯ Volume control ◯ Pressure control ◯ Synchronized intermittent mandatory ventilation (SIMV) ◯ Pressure support ◯ Other
26d. Other ventilator mode:	_____
27d. Leakage compensation:	◯ On ◯ Off
28d. Expiratory time:	_____ (Provide value if available.)
29d. Respiratory rate (breaths/minute):	_____ (Record the patient's natural rate of breathing (breaths/minute))
30d. Respiratory rate (breaths/minute):	_____ (Record the patient's respiratory rate as visible on machine (breaths/minute))
31d. Take picture of brand and model number of oxygen delivery device.	(Please do not include the patient's face in the image)
32d. In the past 24 hours, has the oxygen supply system for this patient changed (new cylinder, new concentrator, etc)?	◯ Yes ◯ No
33d. In the past 24 hours, how many times has pulse oximetry been checked?	_____ (Write in whole numbers without units.)

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Mortality Data

34d. Has patient died since yesterday?

◯ Yes
◯ No

35d. Date of death

_____
(Write in DD/MM/YYYY format.)

This date is not valid, because it is in the future. Please check the information and enter the correct date.

36d. What was the cause of death?

◯ Respiratory
◯ Non-respiratory
◯ Not determined

General comments

37d. Comments

_____

Please mark the form status as "Complete", then "Save & Exit Form"

After completion of this form, please:

Mark this form status as "Complete" Select "Save and Exit Form" Select Form E from the menu to complete the outcome form for this patient

Please mark the form status as "Complete", then "Save & Exit Form"

Time of form completion:

_____
(Tap NOW when form is completed.)

Time to complete form:

_____

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D2_Daily case information (Day 8-30)

Enrolment record ID: _____

Today's date/time _____

1d. Is the patient still in the hospital?
◯ Yes
◯ No

Please mark the form status as "Complete", then "Save & Exit Form"

After completion of this form, please:

Mark this form status as "Complete" Select "Show More Save Options" Select "Save & Go to Next Form" to complete the outcome form (Form E) for this patient

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E_Outcome/completion

Enrolment record ID: _____

Study Completion Information

Time of form start: _____
(Tap NOW when form is started.)

1e. What is the status of the patient in the study?
- ◯ Completed
- ◯ Not completed

2e. Date of end of patient enrolment (completed or not completed) _____
(Write in DD/MM/YYYY format.)

This date is not valid, because it is in the future. Please check the information and enter the correct date.

3e. Reason patient did not complete study:
- ◯ Non-compliance / did not wish to continue in the study
- ◯ Left against medical advice
- ◯ Transferred
- ◯ Otherwise lost to follow up

(Lost to follow up includes patients with unknown or unrecorded outcome.)

4e. Clinical status at hospital discharge:
- ◯ Dead
- ◯ Alive- Clinically improved
- ◯ Alive- Not clinically improved

(Alive- Clinically improved may mean discharged to home, rehab facility, long term care facility; Alive-Not clinically improved may mean transferred to hospice or referral to other hospital.)

5e. At any point in the patient's stay, was any SARS-CoV-2 variant detected on their lab test?
- ◯ Yes
- ◯ No
- ◯ Unknown/Unable to detect SARS-CoV-2 variants at this facility

6e. If yes, which variant was detected?
- ◯ Alpha
- ◯ Beta
- ◯ Gamma
- ◯ Delta
- ◯ Other

7e. Other variant detected: _____

8e. Was the patient discharged from hospital with supplemental oxygen?
- ◯ Yes
- ◯ No

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9e. Select supplemental oxygen source[s]:	☐ Cylinder ☐ Concentrator ☐ Other (Check all that apply.)
10e. Other supplemental oxygen source:	_____
11e. Select oxygen delivery device[s]:	☐ Nasal cannula ☐ Simple face mask ☐ Venturi mask ☐ Non-rebreather mask ☐ CPAP/BiPAP ☐ Other (Check all that apply.)
12e. Other oxygen delivery device:	_____
13e. Was the patient discharged from hospital with a pulse oximeter?	◯ Yes ◯ No

General Comments

14e. Comments	_____
Time of form completion:	_____ (Tap NOW when form is completed.)
Time to complete form:	_____

Please mark the form status as "Complete", then select "Save & Exit Form"

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F_Facility information

Facility ID:	_____
Time form started:	_____ (Press NOW when form is started.)
Name of data access group/facility name:	_____
Identifier of data access group/facility name:	_____
Data collector username	_____

Facility Information

1f. GPS coordinates (Latitude):	_____ (Click "update" when in facility.)
2f. GPS coordinates (Longitude):	_____ (Click "update" when in facility.)

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3f. Country:

- ◯ Argentina
- ◯ Armenia
- ◯ Bangladesh
- ◯ Brazil
- ◯ Colombia
- ◯ Democratic Republic of Congo
- ◯ Egypt
- ◯ El Salvador
- ◯ India
- ◯ Indonesia
- ◯ Iran
- ◯ Jordan
- ◯ Kazakhstan
- ◯ Lebanon
- ◯ Malawi
- ◯ Mongolia
- ◯ Nepal
- ◯ Nigeria
- ◯ Pakistan
- ◯ Papua New Guinea
- ◯ Peru
- ◯ Philippines
- ◯ Republic of Moldova
- ◯ Serbia
- ◯ South Africa
- ◯ Thailand
- ◯ Uganda
- ◯ Uzbekistan
- ◯ Viet Nam

(Begin writing country name and select from dropdown menu.)

4f. Facility name:

- ◯ Cliniques Universitaires De Kinshasa
- ◯ Centre Hospitalier Monkole
- ◯ Clairwood hospital
- ◯ King Edward VIII Hospital
- ◯ Steve Biko Academic Hospital
- ◯ Tshwane District Hospital
- ◯ Federal Medical Centre Abeokuta
- ◯ General Hospital Ijaiye Abeokuta
- ◯ University of Calabar Teaching Hospital
- ◯ General Hospital Calabar
- ◯ Lira Regional Referral Hospital
- ◯ Lira University Hospital
- ◯ Hoima Regional Referral Hospital
- ◯ Entebbe Regional Referral Hospital
- ◯ Queen Elizabeth Central Hospital
- ◯ Chiradzulu Hospital
- ◯ Blantyre District Health Center
- ◯ Hospital Italiano de Buenos Aires
- ◯ Hospital Italiano de San Justo Agustin Rocca
- ◯ COVID-19 Hospital Center/Instituto Nacional de Infectologia Evandro Chagas/Fiocruz
- ◯ Family Health Primary care clinic Manguinhos
- ◯ Hospital das Clínicas of the Federal University of Pernambuco
- ◯ Centro de Pesquisa Clínica / GEP
- ◯ Clínica Colsanitas
- ◯ Puente Aranda
- ◯ Hospital Nacional El Salvador
- ◯ Hospital Nacional Zacamil
- ◯ Hospital de Huaycan
- ◯ Centro de Salud La Fraternidad
- ◯ Kafrelsheikh University
- ◯ Anesthesia and intensive care department
- ◯ Tohid hospital Sanandaj
- ◯ Kamyaran Hospital
- ◯ King Abdulla University Teaching Hospital
- ◯ Princess Basma Hospital
- ◯ Hospital 1, Lebanon
- ◯ Hospital 2, Lebanon
- ◯ Ziauddin university
- ◯ Sheikh Zayed Medical College Rahim Yar Khan
- ◯ Aga Khan University Hospital, Stadium Road, Karachi, Sindh
- ◯ Aga Khan Medical Centre, Gilgit-Baltistan
- ◯ Yerevan State Medical University after Mkhitar Heratsi, Heratsi n. 1 hospital complex
- ◯ Regional Clinical Hospital Karaganda
- ◯ Karaganda Medical University, Medical University Clinic of the NJSC
- ◯ Institute for Emergency medicine IMU, Chisinau
- ◯ Hospital for Communicable diseases
- ◯ Clinical Hospital Medical Center Bezanijska Kosa
- ◯ Zangiata specialized clinic №2 for the treatment of patients with coronavirus infection
- ◯ Ambulance station
- ◯ Chittagong Medical College Hospital
- ◯ Chittagong General Hospital
- ◯ Cumilla Medical College Hospital
- ◯ Hospital 1, Indonesia
- ◯ Hospital 2, Indonesia
- ◯ B P Koirala Institute of Health Sciences
- ◯ Udaypur District Hospital
- ◯ Kirtipur Hospital
- ◯ Primary Health Care Center supported by Phect Nepal
- ◯ Thai Red Cross Emerging Infectious Disease Clinical Center
- ◯ King Chulalongkorn Memorial Hospital
- ◯ Maharaj Nakorn ChiangMai
- ◯ Chiang Mai Neurological Hospital

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	○ Father Muller Medical College Hospital ○ Thumbay Speciality Rural hospital, Father Muller Salvadore Monteiro Rural health centre, Bajpe ○ JSS Medical College ○ District Hospital, Mysuru ○ National Hospital For Tropical Diseases in Hanoi ○ Bac Thang Long Hospital ○ Oxford University Clinical Research Unit ○ Hospital for Tropical Diseases and National Hospital for Tropical Diseases ○ Pacific International Hospital ○ Lae International Hospital ○ State First Central Hospital ○ General hospital of Tuv province ○ Southern Philippines Medical Center ○ Mamay Inn and TTMF facilities in the Davao Region ○ Lung Center of the Philippines (Begin writing facility name and select from dropdown menu.)
5f. City:	_____ (Write full official city name.)
6f. Facility level:	○ First level hospital (District) ○ Second level hospital (Regional/provincial) ○ Tertiary level hospital (Referral/academic) ○ Other
7f. Other facility level:	_____
8f. What is the managing authority of the facility?	☐ Public ☐ Private for profit ☐ Private not for profit ☐ Other (Check all that apply.)
9f. Other managing authority:	_____
10f. Is electricity available 24 hours a day and 7 days a week?	○ Yes ○ No
11f. Facility electricity source:	☐ Grid electricity connection ☐ Generator ☐ Solar ☐ Other (Check all that apply.)
12f. Other electricity source:	_____
13f. Number of total beds in facility:	_____ (Beds = space and mattress/gurneys. Include all bed types (adult and paediatric))

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14f. Number of critical care beds in facility:	_____ (Beds = space and mattress/gurney designated for patients who are critically ill; this should include space for resuscitation and rapid provision of oxygen)
15f. Total number of ventilators in facility:	_____ (This should include all ventilators, including invasive, non-invasive, transport and others.)
16f. Select ventilator types available to this facility:	☐ Invasive mechanical ventilators ☐ CPAP/BiPAP ☐ High flow nasal cannula (HFNC) ☐ Other (including transport) (Check all that apply.)
17f. Number of invasive mechanical ventilators:	_____
18f. Number of CPAP/BiPAP devices:	_____
19f. Number of high flow nasal cannula (HFNC) devices:	_____
20f. Number of other ventilators (including transport):	_____
21f. Is the facility capable of testing or receiving testing information on SARS-CoV-2 variants?	◯ Yes ◯ No ◯ Unknown
22f. Number of biomedical experts (biomedical engineers/clinical engineers/technicians):	_____ (Biomedical experts are professionals who have been trained in the setup, use, maintenance, and troubleshooting of medical devices.)
23f. Number of clinicians who can manage respiratory failure (intubation, mechanical ventilation, management of complications, etc):	_____ (These clinicians may be doctors or nurses who have specialty training in ICU, anaesthesia, emergency medicine, etc.)

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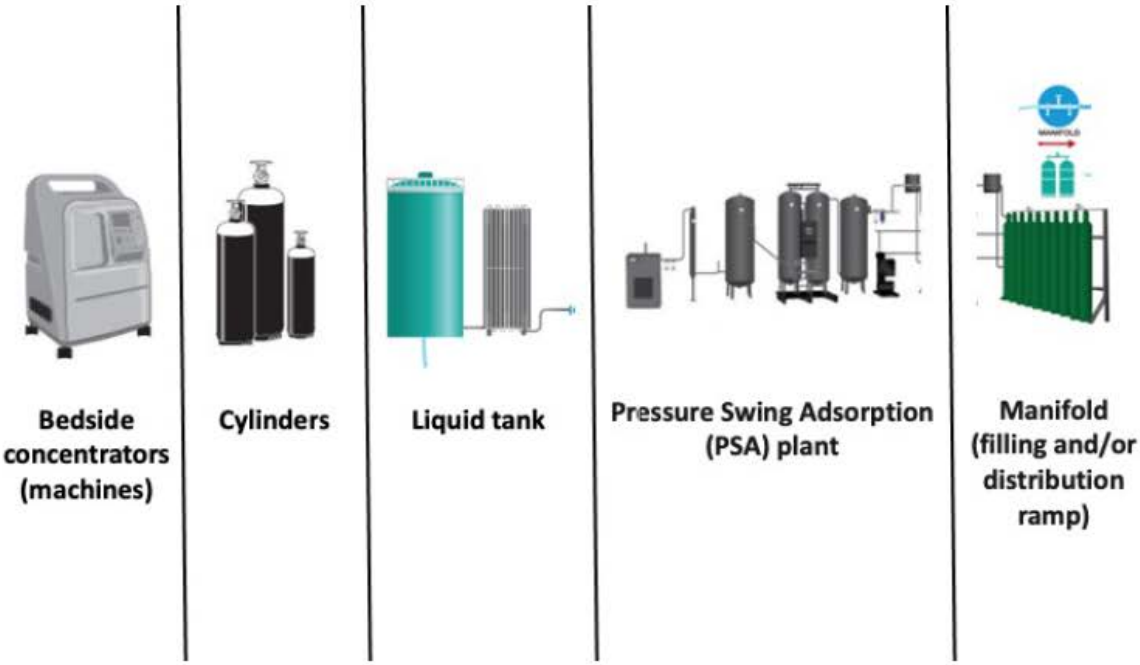
For the following questions, please refer to this image of oxygen supply types.



24f. Which of the following oxygen supply systems are present in the facility?	☐ Bedside concentrators (machines) ☐ Cylinders ☐ Liquid tank system ☐ Piping ☐ PSA system ☐ Manifold (filling and/or distribution ramp) ☐ Other (Check all that apply.)
25f. Other oxygen supply system:	_____
26f. How many concentrators are in the hospital?	_____
27f. What capacity do the concentrators have in litre/minute (L/min)?	☐ 5 L/min ☐ 8 L/min ☐ 10 L/min ☐ Other (Check all that apply.)
28f. Other capacity:	_____ (Write in litres/min.)
29f. Are cylinders filled on site or off site?	☐ On-site ☐ Off-site (Check all that apply.)

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For the following question, please refer to this image of an oxygen outlet:

30f. How many oxygen outlets are there per bed?

_____

(See image above for reference. The color of the oxygen outlet may differ in your country/region.)

31f. What oxygen source is the piping connected to?

☐ PSA system
☐ Liquid tank system
☐ Manifold (distribution ramp)

(PSA=Pressure Swing Adsorption. Check all that apply.)

For the following question, please refer to this image of an oxygen plant:

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32f. What is the PSA system configuration?	◯ Single oxygen generator plants ◯ Duplex oxygen generator plants ◯ Triplex oxygen generator plants ◯ Other (Single generator plants will have a single configuration including only one booster and set of tanks, as in the photo depicted. Duplex generator plants will have two configurations in parallel, including two boosters and set of tanks. These configurations may join at an air compressor junction. Triplex generator plants will have three configurations in parallel, including three boosters and set of tanks. These configurations may join at an air compressor junction.)
33f. Other PSA system configuration:	_____
34f. What is the oxygen production capacity of the PSA system?	_____ (If applicable, write the production capacity of each oxygen generator plant, separated with a semicolon (;). Write number[s] without units.)
35f. Indicate if the oxygen production capacity is recorded in metres cubes/hour(m3/hr) or litres/minute(L/min):	◯ metres cubed/hour (m3/hr) ◯ litres/minute (L/min)
36f. What is the quantity of liquid oxygen contracted for the facility per month?	_____ (Write in whole numbers without units.)
37f. Indicate if the quantity of liquid oxygen is recorded in tons/month, metres cubed(m3)/month, or litres/month:	◯ tons/month ◯ metres cubed (m3)/month ◯ litres/month
38f. Is the PSA plant active 24 hours per day and 7 days per week?	◯ Yes ◯ No (Passive Swing Adsorption (PSA) - generation of enriched oxygenation from ambient air)
39f. How many days per week does the PSA plant function?	_____ (Write number of days without unit label.)
40f. How many hours per day does the PSA plant function?	_____ (Write in number of hours without unit label.)

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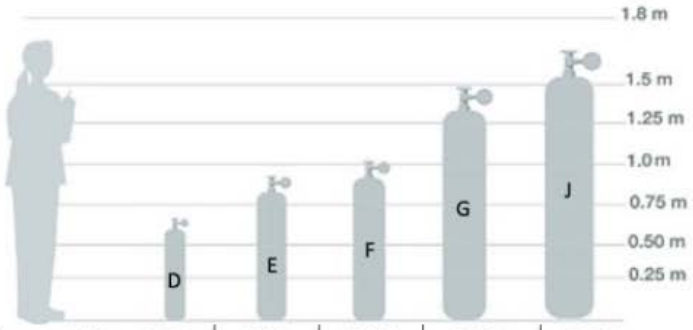
For the following questions, please refer to this image of sizes of oxygen cylinders.



Nominal content [L]:	340 L	680 L	1360 L	3400 L	6800 L
Height x diameter [mm]:	535 x 102	865 x 102	930 x 140	1320 x 178	1520 x 229
Nominal content [m^3]:	0.34 m^3	0.68 m^3	1.36 m^3	3.4 m^3	6.8 m^3
Water capacity [L]:	2.3 L	4.7 L	9.4 L	23.6 L	47.2 L

WHO-UNICEF technical specifications and guidance for oxygen therapy devices:
https://www.who.int/medical_devices/publications/tech_specs_oxygen_therapy_devices/en/

41f. What is the monthly consumption of 340 litre cylinders?

_____ (See above image for reference. Enter number of cylinders. Example: 4. If you do not have this cylinder size, write 0.)

42f. What is the monthly consumption of 680 litre cylinders?

_____ (See above image for reference. Enter number of cylinders. Example: 4)

43f. What is the monthly consumption of 1360 litre cylinders?

_____ (See above image for reference. Enter number of cylinders. Example: 4)

44f. What is the monthly consumption of 3400 litre cylinders?

_____ (See above image for reference. Enter number of cylinders. Example: 4)

45f. What is the monthly consumption of 6800 litre cylinders?

_____ (See above image for reference. Enter number of cylinders. Example: 4)

Annex 4. Statistical Analysis Plan

Statistical analysis plan

Oxygen requirements and approaches to respiratory support in patients with COVID-19 in low- and middle-income countries:
a WHO study

VERSION 2.5
7 December 2022

World Health Organization

Contents

Version control

Version	Approval date	Important changes from previous version	Initials
1.0	15 September 2021	Initial version	SDR
1.1	24 January 2022	Include more states in the multistate model and sample size recalculation	SDR
2.0	23 February 2022	Recalculate sample size and harmonize objectives with research protocol version 5.2, 20 February 2022	SDR
2.2	6 July 2022	Include the scenario of facility level variables as confounders	SDR
2.3	27 October 2022	Recalculate sample size including percentage ICU beds as covariate and correcting GPower input parameters. Include power analysis. Added the two Cox proportional hazard models (patient level and facility level characteristics)	MR
2.4	25 November 2022	Adjust figures according to suggestions made by copyeditor	MR
2.5	7 December 2022	Final technical edit	PR

Notes: Sara Domínguez Rodríguez (SDR): Lead biostatistician (September 2021 – July 2022)
Matthieu Rolland (MR): Lead biostatistician (July 2022 – present)
Pryanka Relan: Global study focal point (2020 – present)

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Abbreviations

BiPAP	bilevel positive airway pressure
CI	confidence interval
COVID-19	SARS-CoV-2 coronavirus disease
CPAP	continuous positive airway pressure
DSMB	Data and Safety Monitoring Board
FiO_2	fraction of inspired oxygen
HFNC	high-flow nasal cannula
HR	hazard ratio
ICU	intensive care unit
IMV	invasive mechanical ventilation
IQR	interquartile range
LMICs	low- and middle-income countries
LPM	litres per minute
LR	logistic regressions
NIPPV	non-invasive positive pressure ventilation
NIV	non-invasive ventilation
OR	odds ratio
PEEP	positive end-expiratory pressure
RR	respiratory rate
SAP	statistical analysis plan
SD	standard deviation
SpO_2	peripheral oxygenation saturation

1. Introduction

Plan objective

This statistical analysis plan (SAP) provides a detailed and comprehensive description of the main, pre-planned analysis for the study "Oxygen requirements and approaches to respiratory support in patients with COVID-19 in low- and middle-income countries: a WHO study". This study has been undertaken by an international research consortium and is fully described in the research protocol version 5.2, 20 February 2022.

This SAP contains a detailed description of data summaries and presentations of statistical results. Major changes in the statistical methodology used for the main and pre-planned analyses would, however, require amendment and re-approval of this SAP by the research consortium and study Data and Safety Monitoring Board (DSMB) or a detailed description and justification in the statistical analysis report.

Study characteristics

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as the cause of a respiratory illness, officially named COVID-19. COVID-19 was described as a pandemic on 11 March 2020.

It is estimated that approximately 20% of those infected with COVID-19 require oxygen supportive therapy. Oxygen is an essential medicine and has been listed as such on the WHO Essential Medicines List and Essential Medicines List for Children. Still, the availability of supplemental medical oxygen in low- and middle-income countries (LMICs) remains a challenge. The COVID-19 pandemic has highlighted, more than ever, the acute need for scale-up of oxygen therapy. WHO has provided an inventory tool to quantify facility-level provision of infrastructure to deliver oxygen therapy. Detailed data on the use of oxygen therapy in LMICs at the patient level remain lacking.

In February 2020, the Research and Development Blueprint for COVID-19 identified key research areas needed for understanding this new disease. Clinical research, including that specifically on the types of respiratory support required by patients, was identified as a key research priority. Since mid 2020, the WHO COVID-19 Clinical Characterization and Management Research Group has been developing two research protocols to support the understanding of respiratory support practices and oxygen requirements for the clinical management of COVID-19.

- The first is an observational study to describe oxygen requirements and respiratory support practices in facilities caring for patients with COVID-19 in LMICs.
- The second is an interventional platform trial which seeks to compare modalities of respiratory support (e.g. continuous positive airway pressure [CPAP], high-flow nasal cannula [HFNC], awake prone position, and other interventions?).

Selection of the most relevant interventions requires an understanding of current practice and expertise in sites that might recruit patients to the trial. Existing studies collect data on oxygen mode of delivery but do not characterize the type, quantity and duration of each modality's use at the patient level, to give a better understanding of oxygen therapy modalities in current use in LMICs.

2. Objectives of the analysis

Overall aim of the study

To describe oxygen use, requirements and respiratory support interventions at the facility level in LMICs. This information will be used to further inform a future platform trial of respiratory support strategies.

Primary objectives

Objective 1.1

Characterize the type and duration of different modalities of oxygen therapy and respiratory support delivered to patients with severe and critical COVID-19.

Objective 1.2

To quantify the duration of stay in, describe practice patterns and transition probabilities across, modes of respiratory support, distinguishing absence, nasal or facial, HFNC, invasive mechanical ventilation (IMV), with death and discharge from hospital as absorbing states.

Secondary objectives

Objective 2.1

To quantify the amount (m^3) of oxygen delivered to patients with severe and critical COVID-19.

Objective 2.2

To describe the demographics and outcomes at hospital discharge of this cohort of hospitalized patients. For this, we will collect minimal demographic information (age, sex, chronic disease and pregnancy), daily oxygen saturation (SpO_2) and respiratory rate (RR), and outcome data at hospital discharge.

Objective 2.3

To describe the resources at the facility level for oxygen delivery and respiratory support. For this, we will collect basic facility-level information about oxygen production, distribution and biomedical equipment availability using the WHO Biomedical Inventory Tool.

Objective 2.4

To describe the impact of facility resources on outcome at hospital discharge. For this, we will collect facility-level information on: electricity, biomedical staff, clinical staff who can manage respiratory failure.

3. Endpoints

Study endpoints for primary objectives

- Total number of patients receiving respiratory support daily and proportion of patients receiving various delivery devices: nasal cannula, face mask, Venturi, non-rebreather, HFNC, CPAP, bilevel positive airway pressure (BiPAP), non-invasive ventilation (NIV), IMV (Objective 1.1).
- The proportion of patients with each of the respiratory supports over the 7 days of follow-up, with subgroup analysis by disease severity, and associations between facility type or patient characteristics (Objective 1.2).

Study endpoints for secondary objectives

- Quantification of total oxygen delivered will be estimated by daily oxygen use for each patient from data collected on flow rates, the fraction of inspired oxygen (FiO_2), positive end-expiratory pressure (PEEP) (Objective 2.1).

- Quantification of total oxygen supply among the 7 days of follow-up stratified by type of device (low-flow oxygen therapy, HFNC, NIV/CPAP and IMV), and region (African, Americas, South-East Asia, European, Eastern Mediterranean and Western Pacific) (Objective 2.1).
- Demographics and outcome characteristics at hospital discharge (Objective 2.2).
- Facility-level information about oxygen production, distribution, biomedical equipment availability (Objective 2.3) and electricity, biomedical staff and clinical staff who can manage respiratory failure (Objective 2.4).

4. Statistical methods for specific objectives

Primary objectives

Summary descriptive

In order to describe the study sample, baseline characteristics and output overall, columns will be included to summarize all subjects within the study (Objective 1.1). In summary tables of continuous variables, interquartile ranges (IQR) and medians will be assessed. In summary tables of categorical variables, counts and percentages will be used. The denominator for each percentage will be the number of subjects within the population group excluding missing observations unless otherwise specified. See **Table 1** and **Table 2** for descriptions of admission characteristics. Chi-squared and Fisher Tests will be performed for categorical variables. For normally distributed continuous variables, the Student T-test will be performed and non-parametric tests such as U-Mann Whitney or Kruskal Wallis when non-normally distributed. All hypothesis testing will be carried out at the 5% significance level and *P* values will be rounded to three decimal places. In summary tables, *P* values less than 0.001 will be reported as < 0.001 as implemented in compareGroups R package *(1).*

Respiratory support transitions

To describe the changes in respiratory support over time (Objective 1.2), Sankey plots will be used to describe patient trajectories, describing the proportion and duration of each type of respiratory support. Kaplan-Meier models will be used to estimate the

probability of each transition during the follow-up time of the study. The hospital outcomes and time to event outcomes will be described in **Table 3**.

A multistate model will be used to study the course of hospital stay of the study population. The focus of the analysis will be on evaluating transitions of escalating respiratory support and transitions to the absorbing states. Multistate models are structures that represent different disease categories or states and the movement of patients between these states (transitions). In this model, summarized in **Fig. 1**, patients may enter the study in one of the three initial transient states: State A: No oxygen therapy or standard oxygen therapy (nasal cannula, face mask or non-rebreather mask); State B: HFNC, NIV or CPAP; and State C: IMV. The model will also include two absorbing states from which a patient no longer transitions: discharge alive and recover (State D) and dead (State E). From State A, a patient can either transition to State B (HFNC/NIV/CPAP), State C (IMV), discharge/recover, or die. From State B (HFNC/NIV/CPAP), a patient can transition into IMV, discharge, or die. From State C (IMV), a patient can transition to discharge/recover or die. Formally the course of a patient's stay is described with a time-in homogeneous Markov chain given by $\{X(t), t \geq 0\}$ with finite state space S = {1, 2, 3, 4, 5, 6, 7, 8, 9} and follow-up time τ. X(t) denotes the state occupied at time t. Various estimands are of interest. We will define the probability to move from one state to another within the multistate model. To perform this multistate model, the *mstate* R package*(2)* will be used to estimate the transition and state occupation probabilities for patients over the course of their hospital stay. The *mstate* package employs Aalen-Johansen estimator based on Markov assumptions.

A multivariable regression model will be used to predict each transition based on the following characteristics: age, gender, vaccination and comorbidities at the time of hospital admission, SpO_2 on the day of the transition, the percentage of intensive care unit (ICU) beds in the facility, and a random intercept at the facility level. The output of the multistate model will be summarized using a forest plot as in **Fig. 2** describing the hazard ratios (HR) and 95% of confidence interval (CI) for each baseline covariate in each transition. Stacked transition probabilities at 7 days after admission will be plotted.

Secondary objectives

The amount of oxygen used for each patient will be computed using the following formula:

- For nasal cannula, face mask and non-rebreather mask, FiO_2 is assumed to be 1.0 and flow rates are adjustable in litres per minute (LPM). Litres per day consumption of oxygen = device flow rate L/minute x 60 minutes/hr x 24 hr/day.

- For HFNC FiO_2 is adjustable (defaulted to 1.0) and flow rate is adjustable in LPM. Litres per day consumption of oxygen = device flow rate L/minute x 60 minutes/hr x 24 hr/day; flow rate in LPM = device flow rate x (FiO_2 - 0.21)/0.79.
- For ventilator, CPAP, BiPAP/non-invasive positive pressure ventilation (NIPPV), FiO_2 is adjustable (defaulted to 1.0) and flow rate is adjustable in LPM and dependent on multiple factors. Liter per day consumption of oxygen = device oxygen consumption rate L/minute x 60 minutes/hr x 24 hr/day. Device oxygen consumption rate in LPM = (minute ventilation + (bias flow x RR x expiratory time/60) + leak) x (FiO_2 - 0.21)/0.79.

This amount of oxygen used for each patient will then be summarized according to oxygen modality, severity and region, as in **Fig. 3**. Different panels will be displayed for box plots summarizing medians and IQR. Comparisons between each stratum will be done using the Kruskal Wallis test (Objective 2.1). Baseline characteristics and overall output columns will be included to summarize all subjects at discharge. In summary tables of continuous variables, IQR and medians will be assessed. In summary tables of categorical variables, counts and percentages will be used. The denominator for each percentage will be the number of subjects within the population group without taking into account missing observations unless otherwise specified. Chi-squared and Fisher Tests will be performed for categorical variables. For normally distributed continuous variables, the Student T-test will be performed and U-Mann Whitney or Kruskal Wallis when non-parametric. All hypothesis testing will be carried out at the 5% significance level and *P* values will be rounded to three decimal places (Objective 2.2). An additional multivariate Cox proportional hazard model will be performed where the outcome is time to death, and the covariates are age, gender, vaccination, comorbidities and SpO_2 at the time of hospital admission, the percentage of ICU beds in the facility, and a random intercept at the facility level. All these covariates will be included in the model and no variable selection process will be performed, as these covariates were all identified as being clinically relevant (Objective 2.2). To describe the oxygen source, distribution, biomedical equipment and oxygen capacity at the facility level, data will be displayed as a whole and summarized by each region and level of facility (Objective 2.3). See **Table 4** for descriptions of oxygen supply at each facility. In summary tables, *P* values less than 0.001 will be reported as < 0.001, as implemented in compareGroups R package *(1).* To assess the impact of facility-level resources, a multivariate Cox proportional hazard model will be performed where the outcome is time to death, and where the covariates will include: electricity, biomedical staff and clinical staff who can manage respiratory failure. All these covariates will be included

in the model and no variable selection process will be performed, as these covariates were all identified as being clinically relevant (Objective 2.4).

Fig. 1. Multistate model

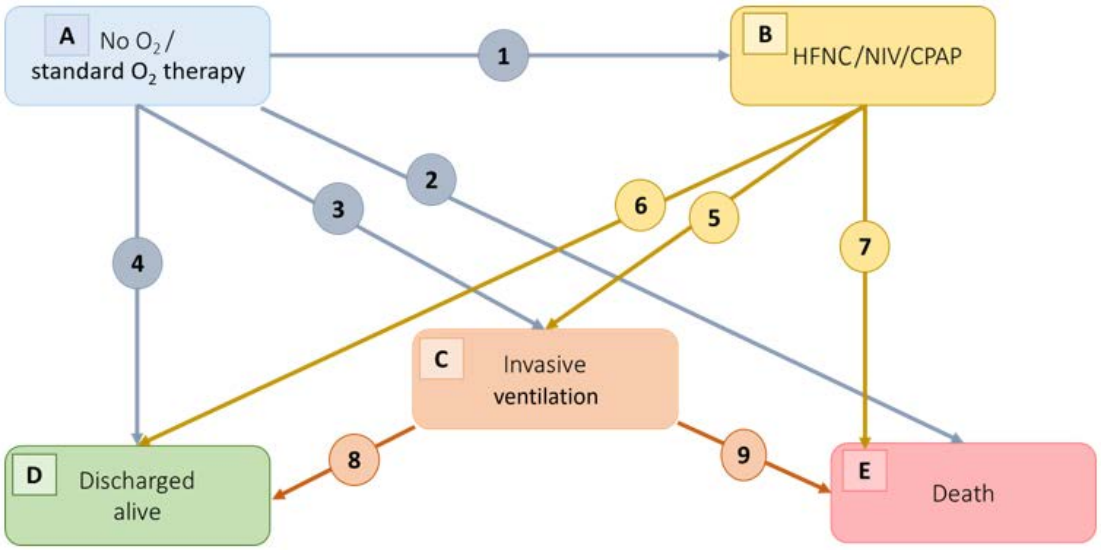

Fig. 2. Output from the multistate model

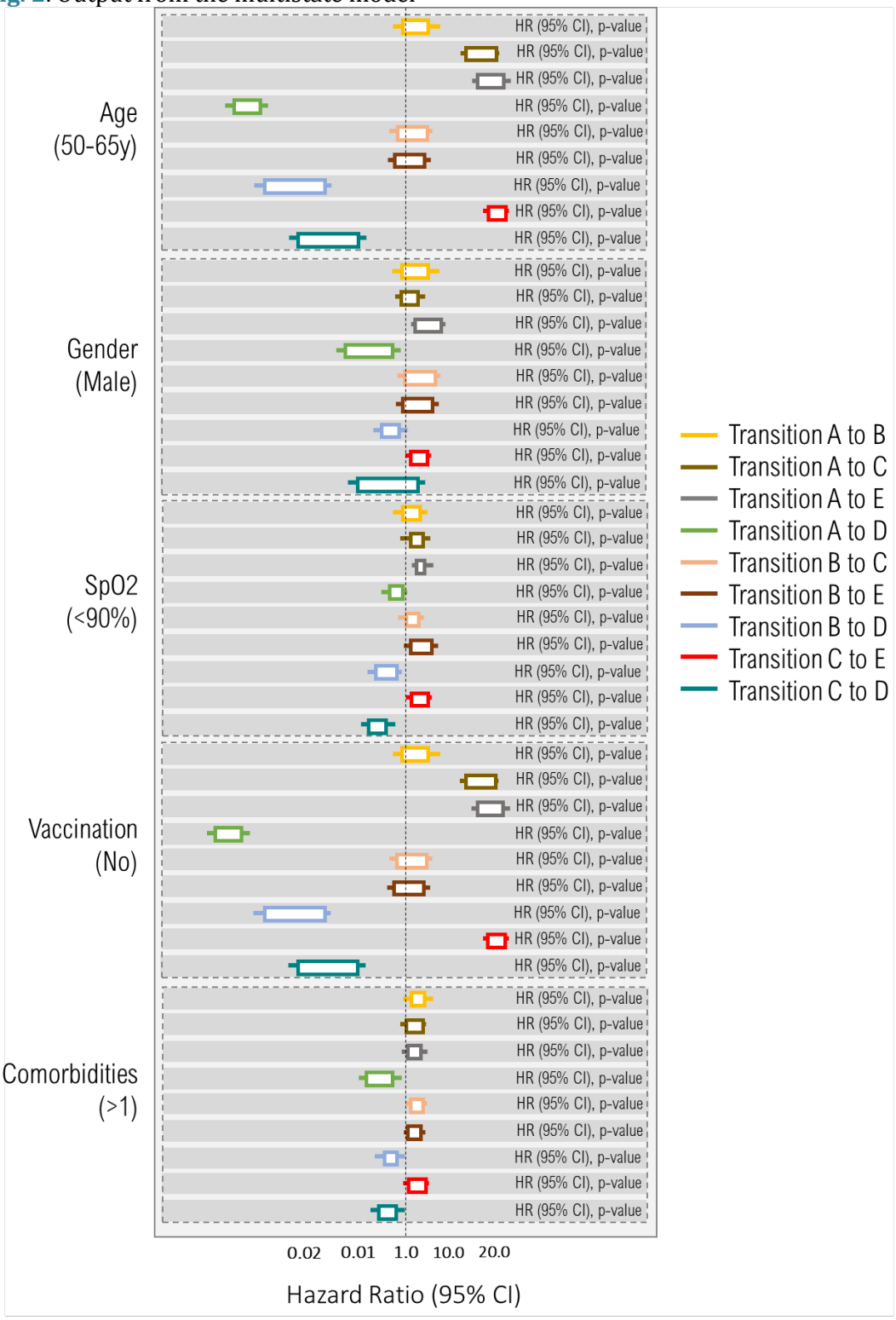

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Fig. 3. Amount of oxygen according to oxygen modality, severity and region

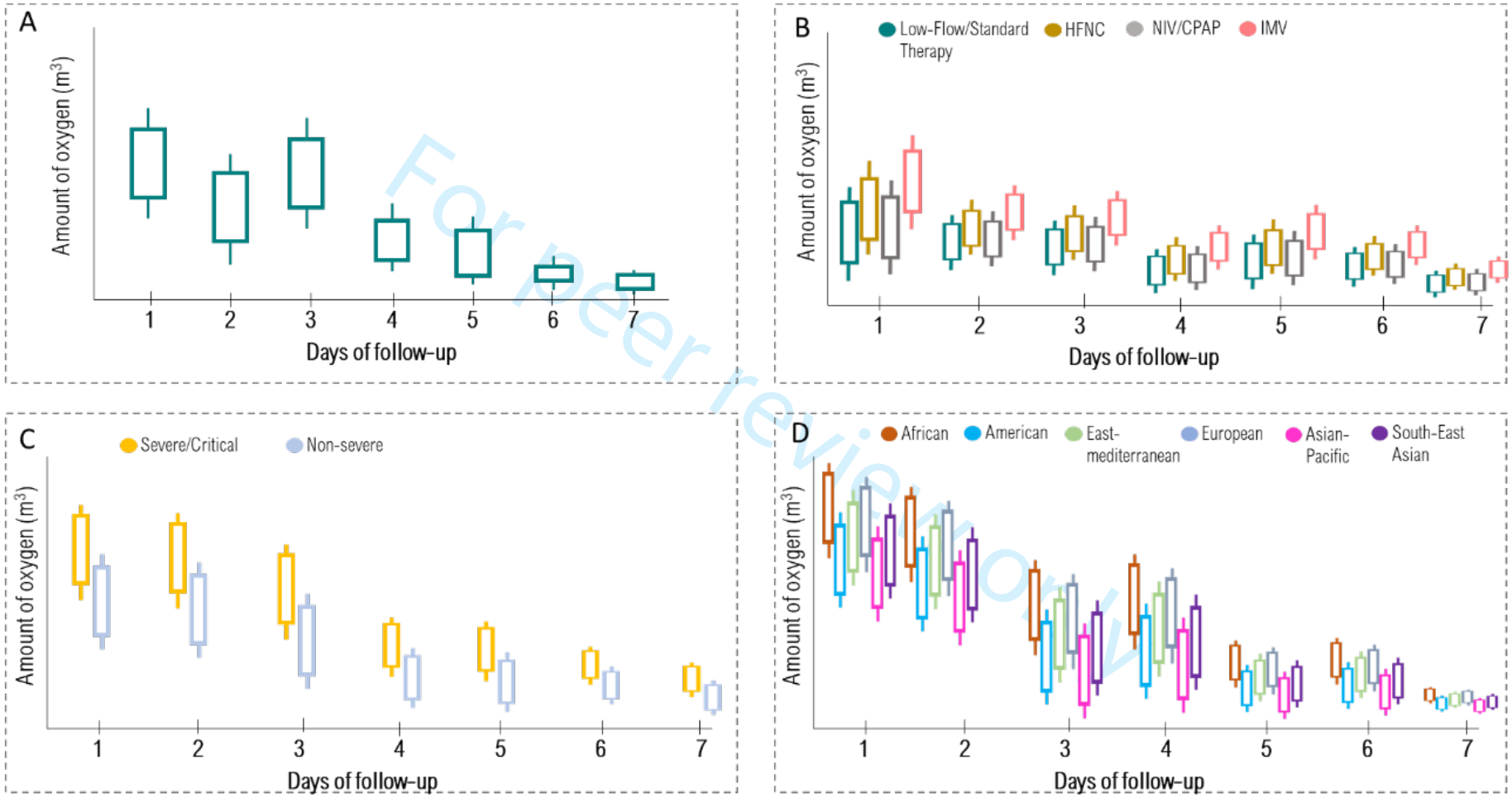

Table 1. Characteristics at admission

Variable	Overall N =
Age	
Years (median, IQR)	
13–17 years	
18 –49 years	
50–69 years	
≥ 70 years	
Gender	
Female (n, %)	
Pregnancy status	
Yes (n,%)	
Admission vital signs	
Heart rate bt/min (median, IQR)	
> 100 bt/min (n, %)	
> 120 bt/min (n, %)	
Respiratory rate b/min (median, IQR)	
> 20 breaths/min (n,%) (adults)	
> 40 breaths/min (n, %) (children)	
Blood pressure mmHg (median, IQR)	
> 140 mmHg (n, %) (adults)	
Oxygen saturation (median, IQR)	
< 90% (n, %)	
< 94% (n, %)	
Mental status	
Alert (n, %)	
Verbal (n, %)	
Pain (n, %)	
Unresponsive scale (AVPU) (n, %)	
Height (cm)	
Weight (kg)	
Body mass index (BMI)	
> 30 (n, %)	
> 40 (n, %)	
Chronic conditions	
None (n, %)	
Chronic cardiac disease (n, %)	
Hypertension (n, %)	
Chronic obstructive pulmonary disease (n, %)	
Asthma (n, %)	
Chronic liver disease (n, %)	
Dementia (n, %)	
Chronic neurological disease (n, %)	
Human immunodeficiency virus (HIV) (n, %)	
Not on ART (n, %)	
Diabetes (n, %)	
Current smoking (n, %)	
Tuberculosis (n, %)	
Asplenia (n, %)	
Cancer (n, %)	
Pathogen testing at any time during hospitalization	
Variant Alpha (n, %)	
Variant Beta (n, %)	
Variant Gamma (n, %)	
Variant Delta (n, %)	
Variant Omicron (n, %)	
Other	
Unknown (n, %)	
Vaccination status	
Vaccinated (n, %)	

Table 2. Respiratory support at hospitalization

Variable	Overall N =
Respiratory and critical care interventions	
Prone position	
Prone (n, %)	
Sitting (fowlers) (n, %)	
Semi-fowlers (n, %)	
Lateral (n, %)	
Lying flat on back (n, %)	
Oxygen therapy	
Flow	
1–5 LPM (n, %)	
6–10 LPM (n, %)	
11–15 LPM (n, %)	
> 15 LPM (n, %)	
Fraction of inspiring oxygen (%)	
Median [IQR]	
Peal airway pressure (cm)	
Median [IQR]	
Positive end-expiratory pressure (cm)	
Median [IQR]	
Respiratory rate (breaths/min)	
Median [IQR]	
Source of oxygen	
Cylinder (n, %)	
Concentrator (n, %)	
Piped/wall oxygen (n, %)	
Other (n, %)	
Oxygen therapy modality	
Room air (n, %)	
Nasal cannula (n,%)	
Simple face mask (n, %)	
Venturi mask (n, %)	
Non-rebreather mask (n, %)	
HFNC (n, %)	
CPAP (n, %)	
Bubble (n, %)	
Nasal pillows (n, %)	
Helmet (n, %)	
Full face mask (n, %)	
BiPAP (n, %)	
Full face mask (n, %)	
Nasal pillows (n, %)	
Helmet (n, %)	
Invasive mechanical ventilation (n, %)	
Other (n, %)	
Ventilator mode	
Volume control (n, %)	
Pressure control (n, %)	
Synchronized intermittent mandatory ventilation (n, %)	
Pressure support (n, %)	
Other (n, %)	

Table 3. Outcomes at hospital discharge

Variable	Overall N =
Hospital outcomes	
Clinical status at discharge	
Death (n, %)	
Alive – clinical improved (n, %)	
Alive – not clinical improved (n, %)	
Lost (n, %)	
Oxygen requirements on discharge	
Yes (n, %)	
Source	
Cylinder (n, %)	
Concentrator (n, %)	
Other (n, %)	
Delivery devices	
Nasal cannula (n, %)	
Simple face mask (n, %)	
Venturi mask (n, %)	
Non-breather mask (n, %)	
CPAP/BiPAP (n, %)	
Other (n, %)	
Patients discharged with pulse oximeter (n, %)	
Time to event outcomes	
Length of hospital stay	
Days from hospital admission until transfer or death	
Days of hospitalization of survivors	
Days of hospitalization of non-survivors	

Table 4. Oxygen supply at each facility

Variable	Overall N =	African Region N =	Region of the Americas N =	South-East Asia Region N =	European Region N =	Eastern Mediterranean Region N =	Western Pacific Region N =
Total beds available							
Median (IQR)							
Total ICU beds available							
Median (IQR)							
Staff dedicated for maintenance of medical equipment							
Yes (n, %)							
Number of staff (n, %)							
Total number of ventilators							
Median (IQR)							
Total number of BiPAP							
Median (IQR)							
Total number of CPAP							
Median (IQR)							
Total number of HFNC							
Median (IQR)							
Back-up generator							
Yes (n, %)							
Grid electricity collection							
Yes (n, %)							
Piped network for medical gases							
Yes (n, %)							
Bedside concentrators							
Yes (n, %)							
Number median (IQR)							
Oxygen cylinders							
Yes (n, %)							
Quantity used monthly							
Liquid oxygen capacity							
Yes (n, %)							
Pressure swing adsorption plant							
Yes (n, %)							

5. Missing data

Records with missing admission dates will be excluded from the analysis. To avoid loss of information and statistical power in the association analysis, missing data will be imputed using a non-parametric random forest imputation algorithm implemented in the missForest R package *(3)*. To prevent too many assumptions, only variables with less than 10% of missing information will be considered for imputation. To get a better understanding of the way missing data distribute among variables in the study, correlation matrixes, patching patterns, and box plot analyses will be performed by means of several functions implemented in MICE and VIM R packages. By checking the missing pattern distribution, missing data would be considered either non-completely at random, missing not at random, or missing at random. Sensitivity analyses on complete cases will be performed.

6. Sample size

The sample sizes to assess associations between each transition and patient's characteristics at the time of hospital admission were calculated.

Because there exists no published method to perform power analysis for multistate models, a priori power analysis was calculated for separate logistic regressions (LR) corresponding to each of the transitions of interest presented in Fig. 1. For each of these LRs, the event of interest was the probability for a patient to go through the transition during their hospitalization. Basal transition rates between states were hypothesized by the Study Steering Committee WHO panel of experts in the reference population, and are summarized in Fig. 4. Basal event rates (Pr Y=1) were derived from these transition rates as summarized in Table 5. Seven covariates were considered (age, gender, vaccination, SpO2, having at least one comorbidity, having more than one comorbidity, and the percentage ICU beds in the facility). A priori distributions for these covariates were estimated using the WHO Global Clinical Platform, as summarized in Table 6. The sample size was estimated to achieve in a two-sided z-test with a α=0.01 to account for the multiple testing incurred, and a power of at least 0.9. The squared multiple correlations for covariates were estimated in a moderate R2=0.2 using the procedure of Demidenko with variance correction (4). G*Power 3.1 Software was used for the estimations (5). No literature was found to estimate odds ratios (ORs) for the percentage ICU beds indicator so sample size was computed for a conservative OR = 2 for each of the transitions.

Table 6 displays the sample size required to estimate the effect of each of age, gender, vaccination, SpO_2, presence of comorbidities and percentage ICU beds on each transition under these assumptions. A chart provided in Fig. 5 shows the achieved power for a given sample size. Table 7 displays the sample size required to estimate the effect of each of the facility level characteristics in the facility level model: electricity availability, number of biomedical experts and number of health care workers who provide direct patient care and can manage patients with respiratory failure on the time to death under these assumptions. A chart provided in Fig. 6 shows the achieved power for a given sample size for this last model. G*Power input parameters are available upon request. The proposed multivariable analysis sample size is N = 1378.

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Fig. 4. The estimated rate of transitions

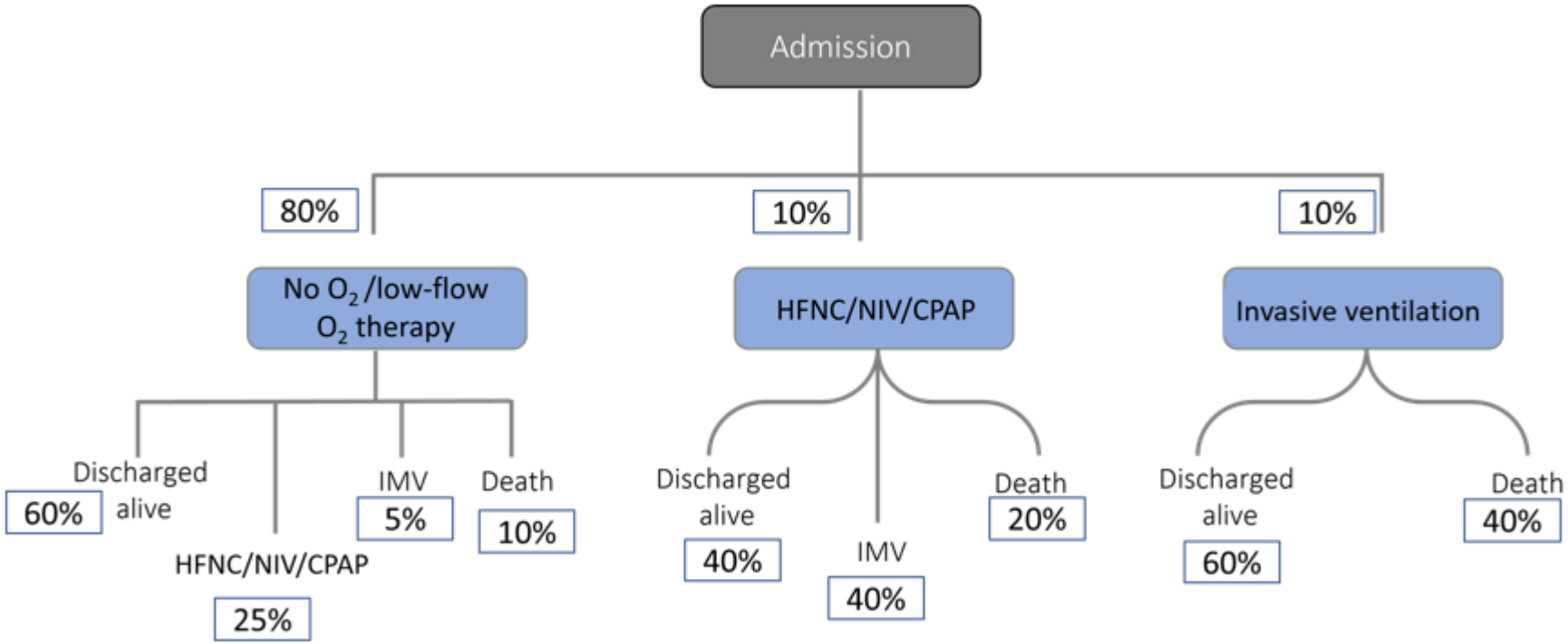


Table 5. Computation of basal event rates based on transition rates described in Fig. 4; the total proportion of admitted patients that will pass through the transition from state A to state B

Transition number in Fig. 1	State A	State B	Among admitted patients, percent to go through state A[a]	Among patients in state A, percent to transition to state B[b]	Basal event rate[c]
1	No O_2/standard O_2 therapy	Non-invasive ventilation	80%	25%	**20.0%**
2	No O_2/standard O_2 therapy	Death	80%	10%	**8.0%**
3	No O_2/standard O_2 therapy	Invasive ventilation	80%	5%	**4.0%**
5	Non-invasive ventilation	Invasive ventilation	30%	40%	**12.0%**
7	Non-invasive ventilation	Death	30%	20%	**6.0%**
9	Invasive ventilation	Death	26%	40%	**10.4%**

[a] Sum of patients to go through a given state, irrespective of their trajectory.
[b] See Fig. 4.
[c] Among all admitted patients, proportion to go through transition A → B = p(A) * p(B).

Table 6. A priori distribution parameters for covariates to be included in the model, necessary for sample size computation

Covariate	Estimated distribution in study population[a]
50–65 year olds	28%
Male	47%
Vaccinated	21%
$SPO_2 < 90\%$	22%
1 comorbidity	28%
> 1 comorbidity	24%

[a] Estimation derived from the WHO Global Clinical Platform.

Table 7. Sample size estimation for each covariate in the multivariable analysis to assess the association with each transition

Probability of transition from No O_2/standard O_2 therapy to HFNC/NIV/CPAP			Reference	Sample size*
	reference	Interest		
Age	*18–29 years old*	*50–65 years old* **4 times higher**	CDC, July 19 2021 *(8)*	N = 227
Gender	*Male*	**3 times higher**	https://www.nature.com/articles/s41467-020-19741-6	N = 309
Vaccination	*No*	**Yes 12 times higher**	https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html#covidnet-hospitalizations-vaccination	N = 96
SpO_2	*> 90%*	*< 89%* **4 times higher**	Mejía F et al., 2021 *(9)*	N = 264
Comorbidity (1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 369
Comorbidity (> 1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 405
% ICU beds	*Continuous*	*+/- 1 SD* **OR = 2**	No literature	N = 265
Probability of transition from No O_2/standard O_2 therapy to death				
Age	*18–29 years old*	*50–65 years old* **35 times higher**	CDC, July 19 2021 *(8)*	N = 51
Gender	*Female*	**3 times higher**	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8270145/	N = 572
Vaccination	*No*	**14 times higher**	https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html#rates-by-vaccine-status	N = 101
SpO_2	*> 90%*	*< 89%* **4 times higher**	Mejía F et al., 2021 *(9)*	N = 436
Comorbidity *(1)*	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 660
Comorbidity (> 1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 720

% ICU beds	*Continuous*	*+/- 1 SD* **OR = 2**	No literature	N = 496
Probability of transition from No O_2/standard O_2 therapy to IMV				
Age	*18–29 years old*	*50 –65 years old* **35 times higher**	CDC, July 19 2021 *(8)*	N = 67
Gender	*Male*	**3 times higher**	https://www.nature.com/articles/s41467-020-19741-6	N = 1038
Vaccination	*No*	**12 times higher**	https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html#covidnet-hospitalizations-vaccination	N = 174
SpO_2	*> 90%*	*< 89%* **4 times higher**	Mejía F et al., 2021 *(9)*	N = 758
Comorbidity (1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 1182
Comorbidity (> 1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 1285
% ICU beds	*Continuous*	*+/- 1 SD* **OR = 2**	No literature	N = 880
Probability of transition from HFNC/NIV/CPAP to IMV				
Age	*18–29 years old*	*50–65 years old* **4 times higher**	CDC, July 19 2021 *(8)*	N = 290
Gender	*Male*	**3 times higher**	https://www.nature.com/articles/s41467-020-19741-6	N = 421
Vaccination	*No*	**12 times higher**	https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html#covidnet-hospitalizations-vaccination	N = 99
SpO_2	*> 90%*	*< 89%* **4 times higher**	Mejía F et al., 2021 *(9)*	N = 334
Comorbidity (1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 492
Comorbidity (> 1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 538

% ICU beds	*continuous*	*+/- 1 SD* **OR = 2**	No literature	N = 367
Probability of transition from HFNC/NIV/CPAP to death				
Age	*18–29 years old*	*50–65 years old* **35 times higher**	CDC, July 19 2021 *(8)*	N = 55
Gender	*Male*	**3 times higher**	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8270145/	N = 726
Vaccination	*No*	**14 times higher**	https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html#rates-by-vaccine-status	N = 116
SpO_2	*> 90%*	*< 89%* **4 times higher**	Mejía F et al., 2021 *(9)*	N = 542
Comorbidity (1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 833
Comorbidity (> 1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 907
% ICU beds	*Continuous*	*+/- 1 SD* **OR = 2**	No literature	N = 624
Probability of transition from IMV to death				
Age	*18–29 years old*	*50–65 years old* **35 times higher**	CDC, July 19 2021 *(8)*	N = 49
Gender	*Male*	**3 times higher**	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8270145/	N = 467
Vaccination	*No*	**14 times higher**	https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html#rates-by-vaccine-status	N = 92
SpO_2	*> 90%*	*< 89%* **4 times higher**	Mejía F et al., 2021 *(9)*	N = 365
Comorbidity (1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 543
Comorbidity (> 1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 593
% ICU beds	*Continuous*	*+/- 1 SD* **OR = 2**	No literature	N = 407

Fig. 5. Achieved power vs sample size for the multistate model

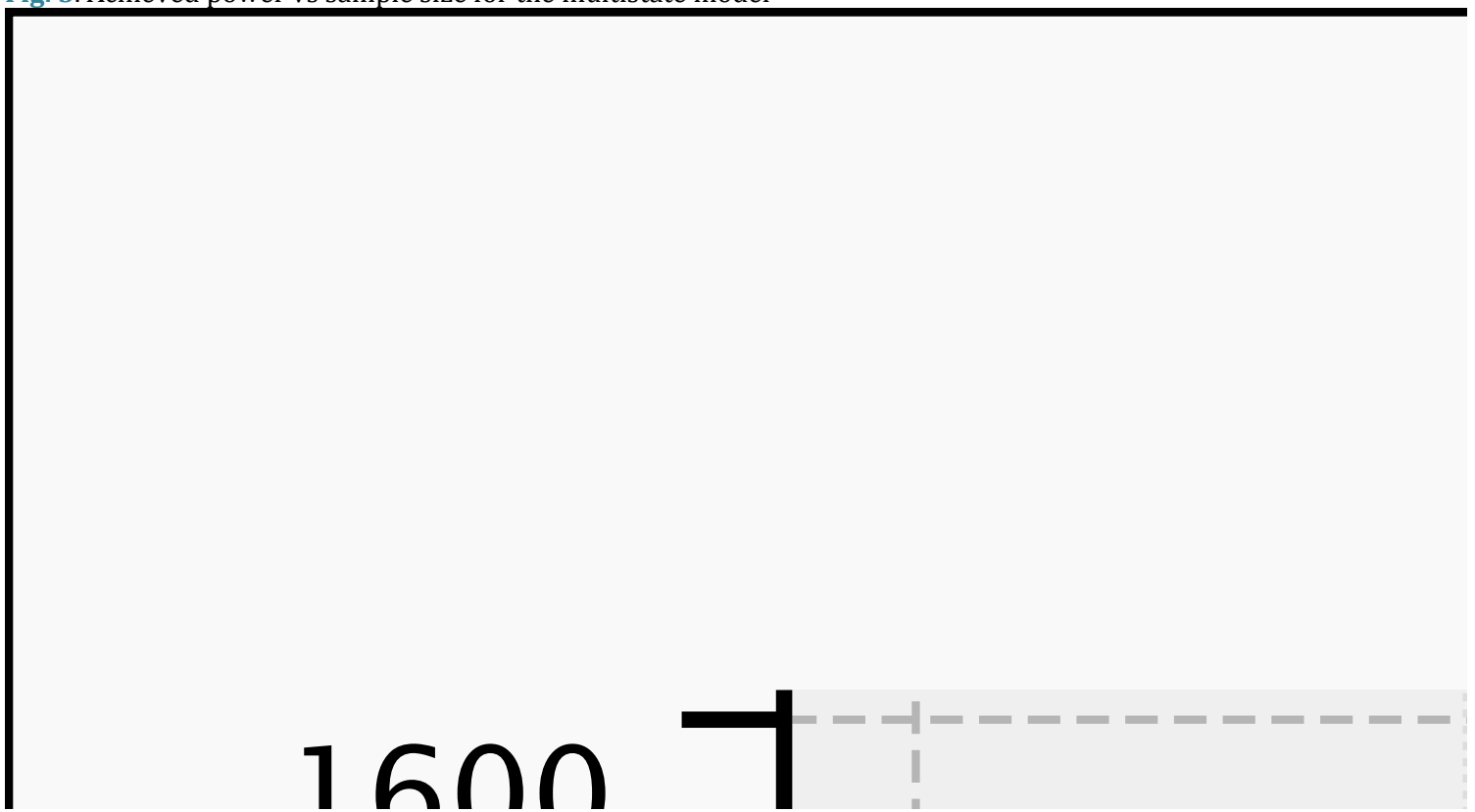
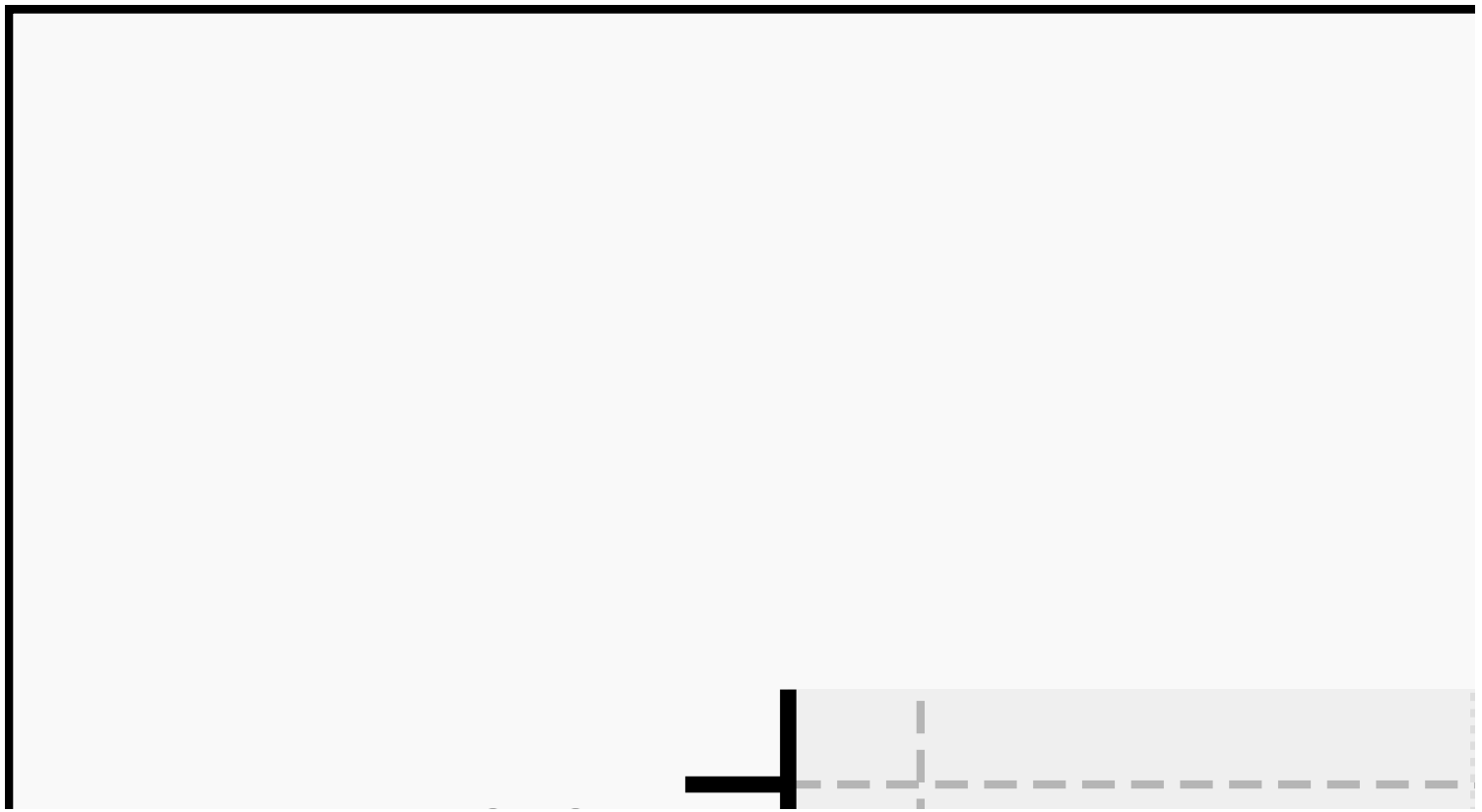


Table 8. Sample size estimation for each covariate in the multivariable analysis to assess the association with death

	Probability of death		Reference	Sample size
	Reference	Interest		
Electricity	*No* 5% event rate	*Yes* **5 times higher**		N = 634
Biomedical staff	*> 90%* 5% event rate	*< 89%* **4 times higher**	Mejía F et al., 2020 *(9)*	N = 852
Any clinical staff who can manage respiratory failure	*No* 5% event rate	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 1378

Fig. 6. Achieved power vs sample size for the facility level model



7. Statistical software

All analyses will be conducted in R (*R: a language and environment for statistical computing*. R Core Team, R Foundation for Statistical Computing, Vienna, Austria; 2020 (https://www.R-project.org) *(7).*

References

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World Health Organization

Annex 5. Data sharing agreement

DATA-SHARING AGREEMENT

Schedule of particulars

This Data-Sharing Agreement is comprised of: (i) this Schedule of Particulars; (ii) Annex I – General Conditions; and (iii) Annex II – Project Description (together, the "**Agreement**").

Pursuant to the terms of this Agreement, the Contributor hereby agrees to provide, and WHO hereby agrees to accept, the Data for the Purpose of Use and subject to the Restrictions on Use.

In this Agreement, the following expressions have the following meanings:

1. The " **Contributor**": [full legal name of your institution];
2. "**WHO**": the World Health Organization, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland;
3. The "**Data**": Any data, results and reports, unpublished or otherwise, collected during or resulting from the Project which are owned by the Contributor and provided by the Contributor to WHO during the term of this Agreement;
4. The "**Parties**": the Contributor and WHO;
5. The "**Project**" as further described in Annex II;
6. The "**Purpose of Use**": The Data are provided to WHO for WHO to implement the Project which is summarized in Annex II and for use in related materials and activities, including but not limited to WHO's internal research purposes;
7. The "**Restrictions on Use**": The Data shall not be used for any purpose other than the Purpose of Use;
8. The "**Term of Agreement**": [Unrestricted in time]; and
9. "**Data Charges**": The Data will be provided free of charge.

Acknowledged and agreed:

Signed for and on behalf of WHO		Signed for and on behalf of the Contributor
Name:	Janet Diaz	Name:
Title:	Lead, Clinical Management for COVID-19	Title:
Date:		Date:

DATA-SHARING AGREEMENT

Annex I – General Conditions

1. Use

1.1. The Data are supplied by the Contributor to WHO solely for the Purpose of Use and subject to the Restrictions on Use.

1.2. Other than for and within the Purpose of Use, the Data shall not be transferred, sold, offered for sale or otherwise used, without the prior written agreement of the Contributor.

1.3. WHO shall only allow parties who have a need to know for the Purpose of Use and who are bound by similar obligations of confidentiality and restrictions on use as contained in this Agreement to have access to the Data.

1.4. In implementing the Purpose of Use, WHO will: not attempt to identify or contact research participants included in the Data; Respect the confidentiality of the Data; and maintain the Data in a secure location on a password-protected, WHO-internal network protected by standard encoding and the WHO firewall for the duration of the Purpose of Use.

2. Confidentiality

2.1. The Data may incorporate confidential information of the Contributor. Accordingly, if and to the extent any such Data are clearly marked by the Contributor as "confidential", WHO shall during the term of this Agreement and for a period of five years following its termination, treat such Data confidential and only disclose them under like obligations of confidentiality and restrictions on use as those contained herein. WHO shall be deemed to have fulfilled its obligations, if it exercises at least the same degree of care in maintaining confidentiality as it would in protecting its own confidential information.

2.2. However, the above mentioned obligations of confidentiality shall not apply to Data which:
(i) can be shown to have been known to WHO at the time of its acquisition from the Contributor; (ii) are acquired from a third party, not in breach of any obligation of confidentiality to the Contributor; (iii) are independently devised or arrived at by, on behalf of, or for WHO without access to the Information; or (iv) enter the public domain otherwise than by breach of the undertakings set out in this Agreement.

3. Rights

3.1. Except for the rights explicitly granted to WHO hereunder, nothing contained in this Agreement shall be construed as conveying any rights under any patents or other intellectual property which either party may have or may hereafter obtain.

3.2. Nothing contained in this Agreement shall restrict the Contributor's right to sell, transfer, assign or distribute the Data to any other person for commercial or non-commercial purposes.

4. Publications

4.1. Subject to the Contributor's proprietary rights, the results obtained through use of the Data within the Purpose of Use may be published by WHO and/or parties collaborating with WHO. In order to avoid prejudice to the Contributor's proprietary rights, WHO shall transmit any material intended to be published or relevant portions thereof, to the Contributor under confidential cover for review at least ten days prior to its submission to any editor, publisher, referee or meeting organizer. In absence of any objection by

the Contributor within that thirty-day period concerning prejudice to its proprietary rights, the publication may proceed, provided, however, that the Contributor shall be duly acknowledged in such publication.

4.2. WHO will prepare manuscript(s) of the results of the Purpose of Use for publication, pursuant to the terms of the applicable protocol, and publish such manuscripts pursuant to WHO's rules and regulations, including its policy on open access, as contained at: http://www.who.int/about/policy/en/. WHO may further use the results of the Purpose of Use to update relevant WHO recommendations and develop any guidelines, including publication thereof, and may further publish those results.

4.3. If a manuscript of the Research Activities is submitted for publication, WHO will in all events retain the Data until the peer review process is completed, and then for one year after publication to ensure sufficient time to address any required responses to the findings (e.g., letters to the editor).

4.4. WHO will ensure that all publications relating to the Data will appropriately acknowledge WHO, the Contributor, and all other entities contributing data to the publication.

5. Undertakings of the Contributor

5.1. The Contributor represents and warrants that: It has obtained all rights and permissions necessary to transfer the Data to WHO and for WHO to implement the Purpose of Use and all other activities relating to the Data as described herein; The Data have been collected from clinical trials, observational studies, or surveillance systems that have been conducted in accordance with all applicable laws.

5.2. Prior to transmitting the Data to WHO, the Contributor will: Verify whether approval from their local/relevant Ethics Review Committee is required for the use of the Data for the Purpose of Use, and if that approval is required, obtain it; and Anonymize all participant-level data in the Data, pursuant to agreed standards, to remove all information in the Data that could be used to identify research participants.

5.3. The Contributor will transmit the Data to WHO securely, using secure file transfer protocol.

5.4. The Contributor will avoid providing to WHO any information relating to the Data or the Research Activities that relates to a natural person, which, either directly or indirectly, in combination with other information available or likely to be available to WHO, can identify such natural person.

5.5. The Contributor makes no warranty of the fitness of the Data for any particular purpose or any other warranty, either express or implied. However, to the best of the Contributor's knowledge, the use of the Data within the Purpose of Use shall not infringe on the proprietary rights of any third party.

5.6. WHO agrees that (except as may explicitly be provided in this Agreement) the Contributor has no control over the use that is made of the Data by WHO or parties collaborating with WHO in accordance with the terms of this Agreement. Consequently, WHO agrees that the Contributor shall not be liable for such use.

6. Other Matters

6.1. Nothing in this Agreement shall be interpreted as establishing a partnership between the parties or establishing one party as the agent of the other or conferring a right on one party to bind the other, except as may be specifically set out herein.

6.2. Without the prior written approval of the other Party, neither Party shall, in any statement or material of an advertising or promotional nature, refer to this Agreement or the relationship between the Parties, or use the name (or any abbreviation thereof) and/or emblem of the other Party.

6.3. Any dispute relating to the interpretation or application of this Agreement shall, unless amicably settled, be subject to conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the parties or, in the absence of agreement, with the rules of arbitration of the International Chamber of Commerce. The Parties shall accept the arbitral award as final.

6.4. Nothing contained herein shall be construed as a waiver of any of the privileges and immunities enjoyed by WHO under national or international law and/or as submitting WHO to any national court or jurisdiction.

6.5. This Agreement sets forth the entire understanding between the parties and supersedes any prior agreements, written or verbal related to the Data. It shall only be capable of change by written amendment executed by duly authorized officers of the Parties.

DATA-SHARING AGREEMENT

Annex II – Project Description

Oxygen requirements and approaches to respiratory support in patients with COVID-19 in low- and middle-income countries: an observational study.

Background: The COVID-19 pandemic has highlighted, more than ever, the acute need for scale up of oxygen therapy. WHO has provided an inventory tool to quantify facility-level provision of infrastructure to deliver oxygen therapy. However, data on the use of oxygen therapy at the patient-level remains lacking.

Population studied: Suspected or confirmed COVID-19 patients receiving oxygen therapy.

Study design: We propose to conduct an observational study of patients with suspected or confirmed COVID-19 receiving oxygen therapy. Basic information and risk factor information will be collected from participants. Participants will be followed for 7 days or until outcome (hospital discharge or death).

Outcomes and analyses: Determination of the person-time on specific respiratory modalities (nasal cannula, face mask, Venturi, NRB, HFNC, CPAP, BiPAP, invasive mechanical ventilation); Proportion of patients on each respiratory modality; Facility oxygen supply metrics; Outcome of patient as measured by WHO clinical progression scale, censored at 30 days.

Please refer to the specific protocol and relevant documents (questionnaire, health care facility questionnaire). For questions contact: covidrespstudy@who.int

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	1

Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	#4	Present key elements of study design early in the paper	4-5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for	7

		for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	6-7
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6-7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	6-7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	
Statistical methods	#12c	Explain how missing data were addressed	6
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	
Statistical methods	#12e	Describe any sensitivity analyses	6
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for	N/a – will be done for results, this is a protocol

		for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	N/a – will be done for results, this is a protocol
Participants	#13c	Consider use of a flow diagram	
N/a – will be done for results, this is a protocol			
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	N/a – will be done for results, this is a protocol
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
N/a – will be done for results, this is a protocol			
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
N/a – will be done for results, this is a			

protocol			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
N/a – will be done for results, this is a protocol			
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/a – will be done for results, this is a protocol
Main results	#16b	Report category boundaries when continuous variables were categorized	N/a – will be done for results, this is a protocol
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
N/a – will be done for results, this is a protocol			
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	

Discussion			
Key results	#18	Summarise key results with reference to study objectives	N/a – will be done for results, this is a protocol
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	N/a – will be done for results, this is a protocol
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	N/a – will be done for results, this is a protocol
Generalisability	#21	Discuss the generalisability (external validity) of the study results	6
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

BMJ Open

WHO O2CoV2: Oxygen requirements and respiratory support in patients with COVID-19 in low- and middle-income countries – protocol for a multi-country, prospective, observational cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-071346.R1
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Primary Subject Heading:	Emergency medicine
Secondary Subject Heading:	Global health, Health policy, Intensive care, Public health, Infectious diseases
Keywords:	COVID-19, INTENSIVE & CRITICAL CARE, ACCIDENT & EMERGENCY MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine), Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Title

WHO O2CoV2: Oxygen requirements and respiratory support in patients with COVID-19 in low- and middle-income countries – protocol for a multi-country, prospective, observational cohort study

Authors

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**WHO O2CoV2 International Study Steering Committee: Gasim Amrahli, John Appiah, Diptesh Aryal, Neale Batra, Kieran Bligh, Devasahayam J Christopher, Mohammed Derow, Laura Alejandra Velez Ruiz Gaitan, Itziar Carrasco Garcia, Bridget Griffith, Christophe Guitton, Madiha Hashmi, Rashidatu Kamara, Leticia Kawano-Dourado, Chiori Kodama, Richard Kojan, Gary Kuniyoshi, Arthur Kwizera, Maria Mendes, Dina Pfeifer, Cinzia De Brito Procopio, Ingrid Lara Rendon, Ludovic Reveiz, Elisabeth Riviello, Matthieu Rolland, Amadou Seck, Elizabeth Stanway, Julie Viry, Pushpa Wijesinghe.

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Keywords: Oxygen; emergency care; critical care; Low- and- middle-income countries (LMICs); severe acute respiratory illness (SARI); COVID-19

Abstract (Word count = 296).

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as the cause of the disease officially named COVID-19, primarily a respiratory illness. COVID-19 was characterized as a pandemic on 11 March 2020. It has been estimated that approximately 20% of people with COVID-19 require oxygen therapy. Oxygen has been listed on the WHO Essential Medicines List and Essential Medicines List for children for almost two decades. The COVID-19 pandemic has highlighted, more than ever, the acute need for scale-up of oxygen therapy. Detailed data on the use of oxygen therapy in LMICs at the patient and facility level are needed to target interventions better globally.

Methods and analysis

We aim to include better describe the requirements and use of oxygen at the facility and patient level of approximately 4,500 patients with COVID-19 in 30 countries. Our objectives are specifically to characterize type and duration of different modalities of oxygen therapy delivered to patients; describe demographics and outcomes of hospitalized patients with COVID-19; and describe facility level oxygen production and support. Primary analyses will be descriptive in nature. Respiratory support transitions will be described in Sankey plots and Kaplan-Meier models will be used to estimate probability of each transition. A multi-state model will be used to study the course of hospital stay of the study population, evaluating transitions of escalating respiratory support transitions to the absorbing states.

Ethics and dissemination

World Health Organization AdHoc Covid-19 Research Ethics Review Committee has approved this global protocol. When this protocol is adopted at specific country sites, national ERCs may make require adjustments in accordance with their respective national research ethics guidelines. Dissemination of this protocol and global findings will be open access through peer-reviewed scientific journals, study website, press and online media.

Registration details: Clinicaltrials.gov number NCT04918875.

Article Summary

Strengths and limitations of this study:

- This study is the first global description of oxygen use and respiratory support approaches for patients in low-and-middle income countries.
- The longitudinal study design allows for evaluation of changes in vital signs (including oxygen saturation) and respiratory support modalities over time in the same patient, providing support to generation of inferences of causality.
- The study also describes facility level oxygen supply systems and oxygen capacities. Through a multistate model, transitions of respiratory support modalities at the patient-level may be linked to facility-level oxygen systems or other facility-level characteristics.
- The primary limitation of this study is its implementation at different stages of the pandemic across countries, thus challenging internal validity of decisions made at sites with regard to clinical management and oxygen use.

Word count (excluding title page, abstract, references, acknowledgements): 3095

Introduction:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as the cause of the respiratory disease officially named COVID-19. COVID-19 was declared a Public Health Emergency of International Concern on 30 January 2020 and characterized as a pandemic in March 2020[1].

Since January 2020, it has been estimated that approximately 20% of patients with COVID-19 develop hypoxia and require oxygen supportive therapy. Oxygen is an essential medicine and has been listed as such on the World Health Organization (WHO) Essential Medicines List and Essential Medicines List for children for almost two decades[2,3]. However, in many low and lower-middle income countries, there is inadequate production, supply and use of medical oxygen.

COVID-19 pandemic has highlighted, more than ever, the acute need for scale up of oxygen supply systems. WHO has published a biomedical inventory tool to quantify facility-level infrastructure and resources for the delivery of oxygen[4] and launched a global oxygen access scale up initiative[5]. However, data on the status of oxygen systems, their use and implications of oxygen therapy on patients in low- and middle-income countries remains lacking.

In February 2020, the WHO Research and Development Blueprint for COVID-19 identified key research areas needed for understanding this new disease[6]. One priority area was the types of respiratory support required by patients. To take this forward, the WHO COVID-19 Clinical Characterization and Management research group created a subgroup, the WHO Respiratory Support Research Group, to develop research protocols concerning respiratory support practices and oxygen requirements for the clinical management of COVID-19. Understanding of current practice and available resources in potential sites globally is required.

At the patient level, existing studies collect data on oxygen mode of delivery, but do not characterize the type, quantity and duration of each modality's use and compare transitions across devices[7]. At the facility level, existing studies describe overall hospital surge capacity but do not give an overview of capacities at the country, regional or global level[8]. Given the call for more sustained global efforts to better target interventions for oxygen systems in LMICs, such as through the Lancet Commission on medical oxygen security and others, a more succinct exploration of oxygen use in LMICs is required.[9]

The objectives of O2CoV2 are to: 1) characterize the type and duration of different modalities of oxygen therapy and respiratory support consumed by patients with severe and critical COVID-19 2) describe demographics and outcomes of hospitalized patients with COVID-19 and 3) describe facility level oxygen production capacity. All objectives are aimed to further inform a future WHO-supported platform trial of respiratory support strategies.

Methods and analysis

STROBE cohort reporting guidelines were used. [10]

Study design

The master protocol serves to describe an observational cohort study from June 2021 through June 2023 that will be implemented in 30 countries representing four low-and-middle income countries (LMICs) from each of the six WHO regions, and targeting up to 4 hospitals per country. LMICs will be defined as per 2021 World Bank criteria and codes "UMC", "LMC" and "LIC"[11]:

Code	Description
HIC	World Bank high-income economies (GNI per capita of USD 12,696 or more in 2020)
UMC	World Bank upper middle-income economies (GNI per capita of USD 4,096 - 12,695 in 2020)
LMC	World Bank lower middle-income economies (GNI per capita of USD 1,046 - 4,095 in 2020)
LIC	World Bank low-income economies (GNI per capita of USD 1,045 or less in 2020)

Study site selection

To recruit interest in participation, WHO put out a global call for expressions of interest to global clinical research networks, social media, WHO website and WHO internal communications through headquarters, regional offices, and country offices. An information sheet about the study was provided for public use on WHO study webiste[12]. Expressions of interest were requested to include information about previous experience with WHO and clinical research, research staff, and COVID-19 burden. See Annex 1.

Site selection was conducted by the WHO O2CoV2 International Study Steering Committee (ISSC) in July 2021[13]. Study sites were limited to health facilities where patients with severe and critical COVID-19 are cared for, including hospitals and temporary COVID-19 treatment centres. The following considerations were considered when selecting sites: WHO region of country; income status of the country (per World Bank criteria); previous history of conducting research before; having dedicated research staff; having identified a paired site. The African and American regions underwent sub-regional division prior to site randomization to have at least 1 country within each subregion of the continent. Finally, EOIs were randomized among regions.

Study population and enrolment

Sites are invited to start enrolling patients as soon as possible, considering need for completion of ethical procedures and trainings. Sites began patient recruitment in January 2022 and should continue enrolment until target sample size is reached or maximum 30 days of recruitment, whichever happens first.

Participant eligibility criteria:

1. Age greater than 12 years.
2. Suspected SARS-CoV-2 infection as determined by treating clinical provider or confirmed SARS-CoV-2 infection confirmed virologically in the laboratory by reverse transcription polymerase chain reaction (RT-PCR) via nasopharyngeal or oropharyngeal sample or by SARS-CoV-2 Ag-RDTs that meet the minimum performance requirements of ≥ 80% sensitivity and ≥ 97% specificity compared with a nucleic acid amplification test (NAAT) reference assay.
3. Admitted to health care facility within 24 hours.
4. Receiving supplemental oxygen or showing clinical evidence of need for supplemental respiratory support as reflected in a respiratory rate ≥ 30 breaths per minute or an $SpO_2 \leq 90\%$, $SpO_2 < 94\%$ if any emergency signs are present.

5. Committed to full supportive care.

Study procedures

Screening

Patients will be screened for inclusion over a maximum of 30 days or until the site level sample size is met, whichever comes sooner. During the recruitment window, patients will be screened for inclusion in the study 24 hours per day, 7 days per week, as they enter the facility for acute care in an emergency unit or area of the hospital that functions like an emergency unit. An information note (see Annex 2) about the study will be posted at all potential areas where screening will occur; thus, informing potential patients that they are being screened and may be enrolled in study. A daily screening log (Annex 3) will be maintained to capture daily numbers of patients screened and those that are enrolled.

Observational period

Patients who meet the inclusion criteria for enrolment will be visited once a day for up to 7 days for daily clinical data collection, or until outcome occurs, whichever happens first. Designated study data collector will review the patient bedside chart and observe the patient and surroundings to collect relevant data.

Data collection will occur daily using an electronic case report form (eCRF) and data entry platform (REDCap) on a WHO-provided tablet computer. See Annex 3 for all CRFs.

Follow-up phase

In cases where the patient remains in hospital more than 7 days, then the data collector will visit the patient each additional day until the patient hospital outcome up to 30 days maximum, to assess only vital status, and, at that time, complete the outcome form.

Link to the platform trial

Through the conduct of the cohort study an established dialogue with site investigators will have been established. For the platform trial, expressions of interest to participate in the full trial will be sought and a final decision will be based on site interest and site capacity as determined in this cohort study.

Statistical analysis

All analyses will be conducted in R (R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria 2020, https://www.R-project.org).

Missing data

For each analysis, the denominator will represent data that are available. To impute missing data, random forest imputation will be considered.

Sample size

To maximise statistical power, we aim to recruit as many participants as possible. The larger the sample, the greater the precision and generalization of the results, and thus for descriptive analyses we aim for

at least 125 patients per hospital, a maximum total of 4,500 patients. For inferential analyses, sample size estimates suggest a minimum of 1,380 patients to attain 95% statistical power to achieve hypotheses discussed with the ISSC.

Selection bias

To minimize selection bias, the following are introduced:

a) systematic and randomized site selection procedure (described above);
b) specific objective criteria for participant study eligibility (described above);
c) waiver of informed consent (see ethical considerations).

Outcomes

To characterize the type and duration of different modalities of oxygen therapy and respiratory support consumed by patients with severe and critical COVID-19, the following outcomes will be reported:

- Baseline characteristics of patients;
- Hospital outcomes of patients;
- Total of patients receiving respiratory support daily and proportion of patients receiving various delivery devices: nasal cannula, face mask, Venturi, non-rebreather, HFNC, CPAP, bilevel positive airway pressure (BiPAP), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV).
- Proportion of patients progressing to IMV.
- Description of respiratory support over time, with subgroup analysis by disease severity, and associations between facility type or patient characteristics.
- Quantification of total oxygen requirements will be estimated by daily oxygen use as from data collected on flow rates, fraction of inspired oxygen (FiO_2), positive end expiratory pressure (PEEP).

Sankey plots for patient trajectories will be used to describe the proportion and duration of each type of respiratory support intervention overall and in subgroup of disease severity. Multistate models will be used to quantify duration of stay in, and transition probabilities across, modes of respiratory support distinguishing absence, nasal or facial, HFNC, IMV, with death and discharge from hospital as absorbing states. Multivariable models will be used to predict transition to IMV or death based on patient and facility characteristics at the time of hospital admission. The following characteristics will be considered: age, chronic conditions, need for oxygen on day of transition and facility.

The amount of oxygen used for each patient will be computed using the following formulas:

- For nasal cannula, face mask and non-rebreather mask, FiO2 is assumed to be 1.0 and flow rates are adjustable in litres per minute (LPM). Litres per day consumption of oxygen = device flow rate L/minute x 60 minutes/hr x 24 hr/day.
- For HFNC FiO2 is adjustable (defaulted to 1.0) and flow rate is adjustable in LPM. Litres per day consumption of oxygen = device flow rate L/minute x 60 minutes/hr x 24 hr/day; flow rate in LPM = device flow rate x (FiO2 - 0.21)/0.79.
- For ventilator, CPAP, BiPAP/non-invasive positive pressure ventilation (NIPPV), FiO2 is adjustable (defaulted to 1.0) and flow rate is adjustable in LPM and dependent on multiple factors. Litre per day consumption of oxygen = device oxygen consumption rate L/minute x 60 minutes/hr x 24 hr/day. Device oxygen consumption rate in LPM = (minute ventilation + (bias flow x RR x expiratory time/60) + leak) x (FiO2 - 0.21)/0.79.

To describe oxygen source, distribution and biomedical equipment at facility level and estimated oxygen capacity at the facility level, descriptive statistics for relevant variables and quantification of total oxygen supply at each facility will be determined.

Full statistical analysis plan available in Annex 4.

Study administration

Data collection and management

Standardized case record forms (CRFs) are available and include:

- screening form;
- case identification and demographics form;
- initial case information form;
- daily follow-up form (to be filled in day 2–7 or until outcome if sooner);
- daily vital status form (to be filled in day 8-30 or until outcome if sooner);
- case outcome form; and
- facility form.

WHO will support data management and access to data entry platform REDCap, that will be stored in a secure WHO server housed in Geneva. The WHO team, within the capacity of research strengthening, will support the development of local data platforms. Implementing partners can opt to manage data on site or through the central WHO repository, subject to local circumstances.

Each participant will be linked to an anonymous study ID within the REDCap database. A locally designated data manager will be sent a password-protected copy of the online database (anonymized and without any patient identifiers) for data analysis.

For local data collection which may occur on paper, all data must be stored in a password-protected database or kept in a locked storage in accordance with national regulations. An identification log will be used, and this log will be stored in a secure, locked facility within the study country. The location of and responsibility for local database(s) will be determined on a case-to-case basis and dependent on national regulations.

All essential study documents, including CRFs, will be electronically archived and retained at WHO for 3 years or for the duration required by the national laws and regulations at local research centres. This is to enable completion of the study, to conduct and complete data curation processes, and to finalize the publication and archival process. The sharing of anonymized data will be done using standard WHO data sharing agreements (see Annex 5) with each study site.

Study personnel at sites: roles and responsibilities

- PIs at all sites will be responsible for the submission and approval process of protocols to institutions.
- Study investigator team will be responsible for all aspects of protocol implementation, including screening, enrolment, daily data collection over 7 days, and follow up until hospital discharge, and facility on-time assessment.

- Clinicians and hospital staff at sites will be minimally impacted as separate data collecting personnel should be hired to collect information and not directly interact in patient care.
- If the above is not feasible, the potential source of bias will be acknowledged in the report. Note: excluding such sites would likely result in exclusion of sites with the most limited resources, which is the focus of the study and the trial.

WHO will serve as central coordinator of all sites and staff will support implementation of the study in all sites, including good clinical practice training.

Patient and public involvement statement:

As part of WHO usual practice, public and patients were engaged in the development of this protocol via the WHO Clinical Characterization and Management working group which led to the voluntary formation of the Respiratory Support Research Working Group, who edited this protocol.

Ethics and dissemination

Ethics approval: World Health Organization AdHoc Covid-19 Research Ethics Review Committee (CERC.0040)

Ethics

WHO ERC has determined that this master protocol meets the Council for International Organizations of Medical Sciences (CIOMS) criteria justifying a waiver of consent. When this protocol is adopted at specific country sites, national ERCs may make a different determination regarding consent in accordance with their respective national research ethics guidelines, for example, requiring modified consent or full individual consent as appropriate.

A wavier of consent is suggested, whereupon each study site can then consider consent exemptions according to national ethical review boards (ERBs). We kindly request this for the following reasons:

- **One, the research would not be feasible or practicable to carry out if informed consent were required.** Our objective is to understand current practice, including capacity and limitations. To do this reliably, we need to have rudimentary data on the entire population at risk, and not simply those who are able to provide consent. A biased estimate, such as would result from the requirement that data only be collected from patients who have provided consent, will provide an inaccurate picture of capacity, resources and outcomes at sites which in turn would not only compromise the data, but also pose potential risk to patients recruited to the trial. As well, by virtue of their illness, patients are often unable to provide first-party consent, and third-party consent is challenging because of restrictions on visiting.
- **Two, this research has important social value.** Understanding the nature of the challenge in resource-limited settings is a prerequisite to developing approaches to address these. Respiratory insufficiency is the dominant cause of death for patients with COVID-19, and so understanding its management has compelling social value.
- **Three, this research poses no more than minimal risks to participants.** We seek waiver of consent for data collection only; no specific study interventions will be undertaken. Further we will record only basic physiological data and location in the hospital, and not personal health information that might be identifying or stigmatizing. Finally, all data are anonymized, and linked to patient identity only through a linkage log that will be maintained **securely at study sites.**

- **Four, ERCs at national level will have full authority to request waiver of consent as per national protocols.**
- **Five, an information note will be posted in all areas where potential screening may occur.** Annex 2 is an information note that can be posted in all areas where potential screening may occur and includes simple language that can be translated into local languages for local ERB approval.

It is of the utmost importance that participant confidentiality be maintained throughout the study. This study will use standard methods in order to protect the confidentiality of participants. All study participants will be assigned a unique, pre-defined study identification number by the investigation team for the labelling of questionnaires for attribution of data to an individual subject and study site. The study will remove all identifiers from any data collected for this study at the individual and study site levels. No names or other directly identifying information, including addresses or medical information, will be entered in the regional or global databases. Study identification numbers will be linked to investigator records stored separately in a secured, locked cabinet and making it possible to identify the case in order to correct missing or erroneous data, in accordance with institutional requirements.

Outputs and dissemination

Each site will be invited to share their anonymized data for pooled analysis and will also be able to publish their own data independently. To protect patient identity, any publications or presentations relating to the study will use only aggregate summary data. Further, after obtaining agreement from each study site, the use of the master protocol and harmonized collection of data will allow for pooled analyses, which in turn will contribute to rapid knowledge generation and strengthen the power of the data analysis to make recommendations. Reporting forms of site-specific results is up to individual investigators and should follow Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies and ideally be reported in such a way to allow for comparison of data across different study sites.

At the global level, dissemination will be done in the standard ways to inform clinical management and WHO guideline development work. Findings from the global pooled analysis will be presented in reports and peer-reviewed publications.

Authorship will be determined using accepted international approaches, according to International Committee of Medical Journal Editors recommendations (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html), commensurate to contributions made.

Author Contributions

PR and DA conceived the study and wrote the first draft; PR, JD, SR, JM designed the study. SC and SDR developed the statistical analysis plan. YA, WS, PC co-chaired the O2CoV2 Steering Committee and provided methodologic inputs. The Respiratory Research Working Group reviewed the document, contributed to drafts and made editorial suggestions. The O2CoV2 Steering Committee reviewed the document and made editorial and methodological suggestions. PR, JD, YA, JM, PC, WS, DA, SM approved final version for submission.

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Data statement

All study forms available in Annex 3.

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Competing interests statement

None declared.

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Oxygen requirements and approaches to respiratory support in patients with COVID-19 in low- and middle-income countries: a WHO study

Annexes

Contents

Annex 1. Expression of interest

WHO Respiratory support research in low- and middle-income countries: Expression of interest (to be filled by interested facilities)

The WHO Respiratory Support Research Working Group, part of the Clinical Characterization and Management of COVID-19, has developed protocols for two studies designed to address the optimal respiratory support of patients with severe COVID-19 in LMICs:

1. An observational (cohort) study to understand current practice, limitations, experience and outcomes.

2. A randomized clinical trial to test the ability of a variety of approaches to reduce mortality and the need for intubation and mechanical ventilation.

We are looking for sites who can recruit patients to both the cohort study and the trial. If you and your site are interested in being involved, please provide us with the following information:

Name: _____
Email address: _____
Site(s): _____
City/Region: _____
Country: _____

Have you/your site previously participated in clinical research?
Observational studies: Yes ____ No ____
If yes, approximate number: 1–2 ____ 3–5 ____ 6 or more ____
If yes, were any of the studies you participated in linked to WHO?
Yes ____ No ____
If yes which ones?

Clinical trials: Yes ____ No ____
If yes, approximate number: 1–2 ____ 3–5 ____ 6 or more ____
If yes, were any of the studies you participated in linked to WHO?
Yes ____ No ____
If yes which ones?

Who collects data or recruits patients at your site? (check all that apply)
Medical doctors ____
Nurses ____
Trainees ____
Dedicated research staff ____
Other ____

On average, how many patients with COVID-19 have you admitted monthly in the past 3 months? ____

May we contact you to discuss the opportunity further?
Yes ____ No ____

Any additional comments? _____
Thanks for your input.

Annex 2. Site information sheet for public posting visibly in sites

WHO Respiratory Support Research Working Group Observational Study
Information sheet for public posting at site

The World Health Organization (WHO) is conducting an observational research study of low- and middle-income country (LMIC) sites to examine baseline practices and resources for oxygen and respiratory care for patients with COVID-19.

This study will help the global community understand the current practices around oxygen use and help support a future study about advanced respiratory support interventions.

This site is enrolled in this study.

Patients who meet eligibility criteria will automatically be enrolled in the study. Eligibility criteria are:

1. Have suspected or confirmed COVID-19.
2. 12 years age or older.
3. Determined by treating clinician to require admission to facility.
4. Determined by treating clinician to require oxygen or has fast respiratory rate or low oxygen saturation.

Daily information about patients will be collected for the first 7 days of hospitalization and once again at hospital discharge. If you are discharged before 7 days, then it will be shorter. If you are hospitalized more than 7 days then you will be visited once a day until your discharge.

The types of information collected will be vital signs and details about the type of oxygen support you may be treated with such as how much oxygen are you being treated with, what kind of face mask or pressure mask is being used to give you the oxygen.

World Health Organization

Annex 3. Case report form

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A_Case screening

Screening ID: _____

Date and time screening is initiated _____

Data collector username: _____

Name of data access group/facility: _____

Identifier of data access group/facility: _____

World Health Organization

WHO O2CoV2 Screening Form

1a. How old is the patient? _____
(If patient is under 1 year of age, enter age as "999")

This patient is not eligible for this study. Please thank them for their time and proceed to the next patient for screening by:

Mark this form status as "Complete" Select "Save and Exit Form" Select "Create New Record"

2a. Does the patient have suspected or confirmed SARS-CoV-2 infection, as determined by treating clinical provider?
- ◯ Yes
- ◯ No

This patient is not eligible for this study. Please thank them for their time and proceed to the next patient for screening by:

Mark this form status as "Complete" Select "Save and Exit Form" Select "Create New Record"

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3a. Is this patient being admitted to the health care facility or was the patient admitted to the health care facility in the last 24 hours?	◯ Yes ◯ No (Being admitted is defined as the patient being expected to stay at least overnight.)

This patient is not eligible for this study. Please thank them for their time and proceed to the next patient for screening by:

Mark this form status as "Complete" Select "Save and Exit Form" Select "Create New Record"

4a. Is the patient: Receiving supplemental oxygen OR With a respiratory rate of ≥ 30 breaths per minute OR With a SpO2 ≤ 90% on room air OR With a SpO2 < 94 % and any one of the following emergency signs are present: Obstructed or absent breathing Severe respiratory distress Central cyanosis Shock Coma and/or convulsions	◯ Yes ◯ No

This patient is not eligible for this study. Please thank them for their time and proceed to the next patient for screening by:

Mark this form status as "Complete" Select "Save and Exit Form" Select "Create New Record"

5a. Is the patient committed to full supportive care?	◯ Yes ◯ No (Full supportive care is defined as the patient is amenable to advanced oxygen support, as is able to be provided at the facility.)

This patient is not eligible for this study. Please thank them for their time and proceed to the next patient for screening by:

Mark this form status as "Complete" Select "Save and Exit Form" Select "Create New Record"

This patient is eligible to be enrolled in the study. This patient should now be assigned a linking identifier and proceed to enrolment.

Please enter the patient's linking identifier below then proceed to screening the next patient by:

Mark this form status as "Complete" Select "Save & Exit Form" Select "Create New Record"

6a. Linking identifier:	_____ (Use this field to uniquely identify the patient to the data collector who will continue with enrollment into the study.)

World Health Organization

B_Case Identification Demographics

Enrolment record ID:

Data collector username:

Data access group name:

Data access group identifier (numeric):

Time of form start:

(Tap NOW when form is started.)

Screening identifier:

(Select screening identifier from dropdown list)

1b. Linking identifier:

(Use this field to uniquely identify the patient, from the data collector who screened the patient into the study.)

World Health Organization

WHO O2CoV2 Enrolment Form

2b. Is the patient enrolled in the study?

- ○ Yes
- ○ No

This patient is not enrolled in this study. Please thank them for their time and proceed to the next patient.

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3b. Please include comments or instructions on how to identify the patient for daily follow up here. Please do not write patient name or medical record/chart number.	_____ (Please do not write patient name or medical record/chart number.)
4b. Date of birth:	_____ (Write in DD/MM/YYYY format.)
5b. Age (years):	_____
Age (years) calculated	_____
The date of birth and age provided are not equal. Please check the age and date of birth provided.	
6b. Sex:	○ Female ○ Male ○ Other
7b. Other sex:	_____
8b. Height (centimetres):	_____ (Write in centimetres without unit label.)
9b. Weight (kilograms):	_____ (Write in kilograms without unit label.)
b. BMI	_____
10b. Is the patient pregnant?	○ Yes ○ No
11b. Date of last menstrual period:	_____ (Write in DD/MM/YYYY format.)

Patient's Past Medical History

12b. Chronic cardiac disease (not hypertension)	○ Yes ○ No ○ Unknown
13b. Hypertension	○ Yes ○ No ○ Unknown
14b. Chronic obstructive pulmonary disease (COPD)	○ Yes ○ No ○ Unknown

World Health Organization

15b. Asthma	○ Yes ○ No ○ Unknown
16b. Chronic liver disease	○ Yes ○ No ○ Unknown
17b. Chronic kidney disease (moderate or severe)	○ Yes ○ No ○ Unknown
18b. Chronic neurological disease	○ Yes ○ No ○ Unknown
19b. AIDS or person living with HIV	○ Yes ○ No ○ Unknown
19b-2. Is the patient currently on ART (antiretroviral therapy)?	○ Yes ○ No ○ Unknown
20b. Diabetes mellitus	○ Yes ○ No ○ Unknown
21b. Current smoking	○ Yes ○ No ○ Unknown
22b. Tuberculosis (active and/or previous infection)	○ Yes ○ No ○ Unknown
23b. Asplenia	○ Yes ○ No ○ Unknown
24b. Cancer (any type, active in the past 6 months)	○ Yes ○ No ○ Unknown
25b. Cancer (any type, greater than 6 months remission)	○ Yes ○ No ○ Unknown
26b. Dementia	○ Yes ○ No ○ Unknown
27b. Mental illness (excluding Dementia)	○ Yes ○ No ○ Unknown

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28b. Other	○ Yes ○ No ○ Unknown
29b. Other past medical history:	_____

General Comments

30b. Comments	_____
Time of form completion:	_____ (Tap NOW when form is completed.)
Time to complete form:	_____

Please mark the form status as "Complete", then select "Show More Save Options", then "Save & Go to Next Form"

World Health Organization

C_Initial case information

Enrolment record ID: _____

Initial case information (facility arrival/emergency unit)

Time of form start: _____
(Tap NOW when form is started.)

1c. Date of arrival to this facility: _____
(Write in DD/MM/YYYY format.)

2c. Time of arrival to this facility: _____

3c. Was this patient referred or transferred from another facility?
- ◯ Yes
- ◯ No

4c. Name of facility where patient referred or transferred from: _____

5c. Date of arrival to previous facility: _____
(Write in DD/MM/YYYY format.)

The date entered is not valid, because it is in the future. Please check the information and re-enter the date.

6c. COVID-19 status:
- ◯ Suspected
- ◯ Confirmed

7c. Date of most recent COVID-19 positive test: _____
(Write in DD/MM/YYYY format.)

The date entered is not valid, because it is in the future. Please check the information and re-enter the date.

8c. By which method was the patient's SARS-CoV-2 infection confirmed on [date_covid]?
- ◯ RT-PCR via nasopharyngeal or oropharyngeal sample
- ◯ SARS-CoV-2 Ag-RDTs that meet the minimum performance requirements of ≥80% sensitivity and ≥97% specificity compared to a NAAT reference assay
- ◯ Blood
- ◯ Other method

9c. Other method: _____

10c. Has the patient received a COVID-19 vaccine?
- ◯ Yes
- ◯ No
- ◯ Unknown

World Health Organization

11c. How many COVID-19 vaccines have been received?	○ 1 ○ 2 ○ 3 ○ More than 3
12c. When was the last vaccine received?	_____

General comments

13c. Comments	_____
Time of form completion:	_____ (Tap NOW when form is completed.)

Please mark the form status as "Complete" then select "Show More Save Options", and select "Save & Go to Next Form" to complete the daily data (Form D1) for this patient.

Time to complete form:	_____

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D1_Daily case information (Day 1-7)

Enrolment record ID:	_____
1d. Please select the day of data collection for which you are completing this form.	◯ Day 1 (day of enrolment) ◯ Day 2 ◯ Day 3 ◯ Day 4 ◯ Day 5 ◯ Day 6 ◯ Day 7
Time of form start:	_____ (Tap NOW when form is started.)

Daily, from hospital admission to hospital day number 7

2d. Today's date and current time:	_____ (Write in DD/MM/YYYY H:M:S format.)
3d. Location of patient:	◯ Emergency unit ◯ Ward ◯ ICU ◯ Other
4d. Other location:	_____
5d. Day and time of most recent vital signs:	_____
This day and time is not valid, because it is in the future. Please check the information and enter the correct day and time.	
6d. Mental status (AVPU):	◯ Alert ◯ Verbal ◯ Pain ◯ Unresponsive
7d. Systolic blood pressure (mmHg):	_____ (Write in mmHg, without unit label. Example) "70")
8d. Oxygen saturation:	_____ (Write in %, without % symbol. Example) "70")
9d. Heart rate (beats/minute):	_____ (Write in beats/minute, without unit label. Example) "50")

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10d. Patient positioning:	◯ Prone ◯ Sitting (Fowler's) ◯ Semi-Fowler's ◯ Lateral ◯ Lying flat on back
11d. Oxygen therapy modality:	☐ Room air ☐ Nasal cannula ☐ Simple face mask ☐ Venturi mask ☐ Non-rebreather mask ☐ Hi-flow nasal cannula ☐ CPAP ☐ BiPAP ☐ Intubated ☐ Other
12d. Other oxygen therapy modality:	_____
13d. Oxygen source:	◯ Cylinder ◯ Concentrator ◯ Piped/wall oxygen ◯ Other
14d. Other oxygen source:	_____
15d. Select CPAP type:	◯ Bubble ◯ Nasal pillows ◯ Helmet ◯ Full face mask
16d. CPAP pressure setting:	_____ (Write in cm H2O without unit label. Example) "5")
17d. Select BiPAP type:	◯ Nasal pillows ◯ Helmet ◯ Full face mask
18d. IPAP (inspiratory positive airway pressure):	_____ (Write in cm H2O without unit label. example) "5")
19d. EPAP (expiratory positive airway pressure):	_____ (Write in cm H2O without unit label. Example) "5")
20d. Oxygen flow rate (litres/minute):	_____ (Write in litres/minute, without unit label. Example) "50")
21d. Fraction of inspired oxygen (FiO2):	_____ (Write in %, without % symbol. Example) "50" Reminder: FiO2 of room air is 21%)

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22d. Peak airway pressure (in cm H2O):	_____ (Write in cm H2O without unit label. Example) "50")
23d. Positive end expiratory pressure (in cm H2O):	_____ (Write in cm H2O without unit label. Example) "5")
24d. Tidal volume (in mL):	_____ (Write in mL without unit label. Example) "500")
25d. What is the ventilator mode?	◯ Volume control ◯ Pressure control ◯ Synchronized intermittent mandatory ventilation (SIMV) ◯ Pressure support ◯ Other
26d. Other ventilator mode:	_____
27d. Leakage compensation:	◯ On ◯ Off
28d. Expiratory time:	_____ (Provide value if available.)
29d. Respiratory rate (breaths/minute):	_____ (Record the patient's natural rate of breathing (breaths/minute))
30d. Respiratory rate (breaths/minute):	_____ (Record the patient's respiratory rate as visible on machine (breaths/minute))
31d. Take picture of brand and model number of oxygen delivery device.	(Please do not include the patient's face in the image)
32d. In the past 24 hours, has the oxygen supply system for this patient changed (new cylinder, new concentrator, etc)?	◯ Yes ◯ No
33d. In the past 24 hours, how many times has pulse oximetry been checked?	_____ (Write in whole numbers without units.)

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Mortality Data

34d. Has patient died since yesterday?

◯ Yes
◯ No

35d. Date of death

_____
(Write in DD/MM/YYYY format.)

This date is not valid, because it is in the future. Please check the information and enter the correct date.

36d. What was the cause of death?

◯ Respiratory
◯ Non-respiratory
◯ Not determined

General comments

37d. Comments

_____

Please mark the form status as "Complete", then "Save & Exit Form"

After completion of this form, please:

Mark this form status as "Complete" Select "Save and Exit Form" Select Form E from the menu to complete the outcome form for this patient

Please mark the form status as "Complete", then "Save & Exit Form"

Time of form completion:

_____
(Tap NOW when form is completed.)

Time to complete form:

_____

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D2_Daily case information (Day 8-30)

Enrolment record ID:	_____
Today's date/time	_____
1d. Is the patient still in the hospital?	◯ Yes ◯ No

Please mark the form status as "Complete", then "Save & Exit Form"

After completion of this form, please:

Mark this form status as "Complete" Select "Show More Save Options" Select "Save & Go to Next Form" to complete the outcome form (Form E) for this patient

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E_Outcome/completion

Enrolment record ID: _____

Study Completion Information

Time of form start: _____
(Tap NOW when form is started.)

1e. What is the status of the patient in the study?
- ◯ Completed
- ◯ Not completed

2e. Date of end of patient enrolment (completed or not completed) _____
(Write in DD/MM/YYYY format.)

This date is not valid, because it is in the future. Please check the information and enter the correct date.

3e. Reason patient did not complete study:
- ◯ Non-compliance / did not wish to continue in the study
- ◯ Left against medical advice
- ◯ Transferred
- ◯ Otherwise lost to follow up

(Lost to follow up includes patients with unknown or unrecorded outcome.)

4e. Clinical status at hospital discharge:
- ◯ Dead
- ◯ Alive- Clinically improved
- ◯ Alive- Not clinically improved

(Alive- Clinically improved may mean discharged to home, rehab facility, long term care facility; Alive-Not clinically improved may mean transferred to hospice or referral to other hospital.)

5e. At any point in the patient's stay, was any SARS-CoV-2 variant detected on their lab test?
- ◯ Yes
- ◯ No
- ◯ Unknown/Unable to detect SARS-CoV-2 variants at this facility

6e. If yes, which variant was detected?
- ◯ Alpha
- ◯ Beta
- ◯ Gamma
- ◯ Delta
- ◯ Other

7e. Other variant detected: _____

8e. Was the patient discharged from hospital with supplemental oxygen?
- ◯ Yes
- ◯ No

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9e. Select supplemental oxygen source[s]:	☐ Cylinder ☐ Concentrator ☐ Other (Check all that apply.)
10e. Other supplemental oxygen source:	_____
11e. Select oxygen delivery device[s]:	☐ Nasal cannula ☐ Simple face mask ☐ Venturi mask ☐ Non-rebreather mask ☐ CPAP/BiPAP ☐ Other (Check all that apply.)
12e. Other oxygen delivery device:	_____
13e. Was the patient discharged from hospital with a pulse oximeter?	◯ Yes ◯ No

General Comments

14e. Comments	_____
Time of form completion:	_____ (Tap NOW when form is completed.)
Time to complete form:	_____

Please mark the form status as "Complete", then select "Save & Exit Form"

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F_Facility information

Facility ID:	_____
Time form started:	_____ (Press NOW when form is started.)
Name of data access group/facility name:	_____
Identifier of data access group/facility name:	_____
Data collector username	_____

Facility Information

1f. GPS coordinates (Latitude):	_____ (Click "update" when in facility.)
2f. GPS coordinates (Longitude):	_____ (Click "update" when in facility.)

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3f. Country:

- ◯ Argentina
- ◯ Armenia
- ◯ Bangladesh
- ◯ Brazil
- ◯ Colombia
- ◯ Democratic Republic of Congo
- ◯ Egypt
- ◯ El Salvador
- ◯ India
- ◯ Indonesia
- ◯ Iran
- ◯ Jordan
- ◯ Kazakhstan
- ◯ Lebanon
- ◯ Malawi
- ◯ Mongolia
- ◯ Nepal
- ◯ Nigeria
- ◯ Pakistan
- ◯ Papua New Guinea
- ◯ Peru
- ◯ Philippines
- ◯ Republic of Moldova
- ◯ Serbia
- ◯ South Africa
- ◯ Thailand
- ◯ Uganda
- ◯ Uzbekistan
- ◯ Viet Nam

(Begin writing country name and select from dropdown menu.)

4f. Facility name:

- ◯ Cliniques Universitaires De Kinshasa
- ◯ Centre Hospitalier Monkole
- ◯ Clairwood hospital
- ◯ King Edward VIII Hospital
- ◯ Steve Biko Academic Hospital
- ◯ Tshwane District Hospital
- ◯ Federal Medical Centre Abeokuta
- ◯ General Hospital Ijaiye Abeokuta
- ◯ University of Calabar Teaching Hospital
- ◯ General Hospital Calabar
- ◯ Lira Regional Referral Hospital
- ◯ Lira University Hospital
- ◯ Hoima Regional Referral Hospital
- ◯ Entebbe Regional Referral Hospital
- ◯ Queen Elizabeth Central Hospital
- ◯ Chiradzulu Hospital
- ◯ Blantyre District Health Center
- ◯ Hospital Italiano de Buenos Aires
- ◯ Hospital Italiano de San Justo Agustin Rocca
- ◯ COVID-19 Hospital Center/Instituto Nacional de Infectologia Evandro Chagas/Fiocruz
- ◯ Family Health Primary care clinic Manguinhos
- ◯ Hospital das Clínicas of the Federal University of Pernambuco
- ◯ Centro de Pesquisa Clínica / GEP
- ◯ Clínica Colsanitas
- ◯ Puente Aranda
- ◯ Hospital Nacional El Salvador
- ◯ Hospital Nacional Zacamil
- ◯ Hospital de Huaycan
- ◯ Centro de Salud La Fraternidad
- ◯ Kafrelsheikh University
- ◯ Anesthesia and intensive care department
- ◯ Tohid hospital Sanandaj
- ◯ Kamyaran Hospital
- ◯ King Abdulla University Teaching Hospital
- ◯ Princess Basma Hospital
- ◯ Hospital 1, Lebanon
- ◯ Hospital 2, Lebanon
- ◯ Ziauddin university
- ◯ Sheikh Zayed Medical College Rahim Yar Khan
- ◯ Aga Khan University Hospital, Stadium Road, Karachi, Sindh
- ◯ Aga Khan Medical Centre, Gilgit-Baltistan
- ◯ Yerevan State Medical University after Mkhitar Heratsi, Heratsi n. 1 hospital complex
- ◯ Regional Clinical Hospital Karaganda
- ◯ Karaganda Medical University, Medical University Clinic of the NJSC
- ◯ Institute for Emergency medicine IMU, Chisinau
- ◯ Hospital for Communicable diseases
- ◯ Clinical Hospital Medical Center Bezanijska Kosa
- ◯ Zangiata specialized clinic №2 for the treatment of patients with coronavirus infection
- ◯ Ambulance station
- ◯ Chittagong Medical College Hospital
- ◯ Chittagong General Hospital
- ◯ Cumilla Medical College Hospital
- ◯ Hospital 1, Indonesia
- ◯ Hospital 2, Indonesia
- ◯ B P Koirala Institute of Health Sciences
- ◯ Udaypur District Hospital
- ◯ Kirtipur Hospital
- ◯ Primary Health Care Center supported by Phect Nepal
- ◯ Thai Red Cross Emerging Infectious Disease Clinical Center
- ◯ King Chulalongkorn Memorial Hospital
- ◯ Maharaj Nakorn ChiangMai
- ◯ Chiang Mai Neurological Hospital

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	○ Father Muller Medical College Hospital ○ Thumbay Speciality Rural hospital, Father Muller Salvadore Monteiro Rural health centre, Bajpe ○ JSS Medical College ○ District Hospital, Mysuru ○ National Hospital For Tropical Diseases in Hanoi ○ Bac Thang Long Hospital ○ Oxford University Clinical Research Unit ○ Hospital for Tropical Diseases and National Hospital for Tropical Diseases ○ Pacific International Hospital ○ Lae International Hospital ○ State First Central Hospital ○ General hospital of Tuv province ○ Southern Philippines Medical Center ○ Mamay Inn and TTMF facilities in the Davao Region ○ Lung Center of the Philippines (Begin writing facility name and select from dropdown menu.)
5f. City:	_____ (Write full official city name.)
6f. Facility level:	○ First level hospital (District) ○ Second level hospital (Regional/provincial) ○ Tertiary level hospital (Referral/academic) ○ Other
7f. Other facility level:	_____
8f. What is the managing authority of the facility?	☐ Public ☐ Private for profit ☐ Private not for profit ☐ Other (Check all that apply.)
9f. Other managing authority:	_____
10f. Is electricity available 24 hours a day and 7 days a week?	○ Yes ○ No
11f. Facility electricity source:	☐ Grid electricity connection ☐ Generator ☐ Solar ☐ Other (Check all that apply.)
12f. Other electricity source:	_____
13f. Number of total beds in facility:	_____ (Beds = space and mattress/gurneys. Include all bed types (adult and paediatric))

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14f. Number of critical care beds in facility:	_____ (Beds = space and mattress/gurney designated for patients who are critically ill; this should include space for resuscitation and rapid provision of oxygen)
15f. Total number of ventilators in facility:	_____ (This should include all ventilators, including invasive, non-invasive, transport and others.)
16f. Select ventilator types available to this facility:	☐ Invasive mechanical ventilators ☐ CPAP/BiPAP ☐ High flow nasal cannula (HFNC) ☐ Other (including transport) (Check all that apply.)
17f. Number of invasive mechanical ventilators:	_____
18f. Number of CPAP/BiPAP devices:	_____
19f. Number of high flow nasal cannula (HFNC) devices:	_____
20f. Number of other ventilators (including transport):	_____
21f. Is the facility capable of testing or receiving testing information on SARS-CoV-2 variants?	◯ Yes ◯ No ◯ Unknown
22f. Number of biomedical experts (biomedical engineers/clinical engineers/technicians):	_____ (Biomedical experts are professionals who have been trained in the setup, use, maintenance, and troubleshooting of medical devices.)
23f. Number of clinicians who can manage respiratory failure (intubation, mechanical ventilation, management of complications, etc):	_____ (These clinicians may be doctors or nurses who have specialty training in ICU, anaesthesia, emergency medicine, etc.)

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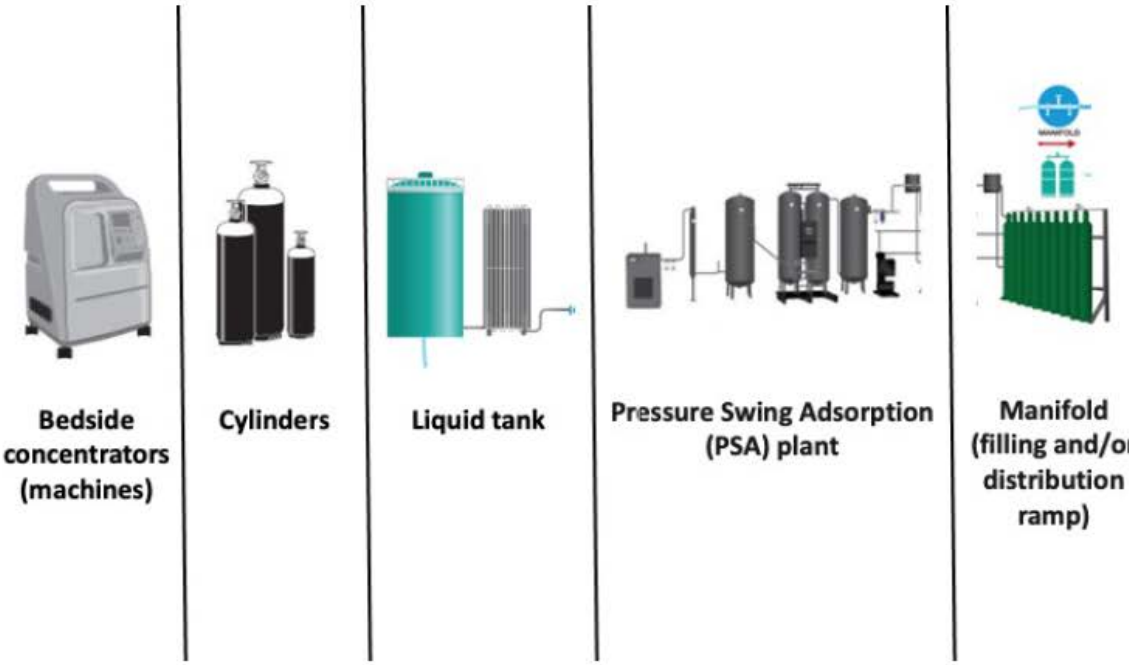
For the following questions, please refer to this image of oxygen supply types.



24f. Which of the following oxygen supply systems are present in the facility?

- ☐ Bedside concentrators (machines)
- ☐ Cylinders
- ☐ Liquid tank system
- ☐ Piping
- ☐ PSA system
- ☐ Manifold (filling and/or distribution ramp)
- ☐ Other

(Check all that apply.)

25f. Other oxygen supply system: _____

26f. How many concentrators are in the hospital? _____

27f. What capacity do the concentrators have in litre/minute (L/min)?

- ☐ 5 L/min
- ☐ 8 L/min
- ☐ 10 L/min
- ☐ Other

(Check all that apply.)

28f. Other capacity: _____

(Write in litres/min.)

29f. Are cylinders filled on site or off site?

- ☐ On-site
- ☐ Off-site

(Check all that apply.)

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For the following question, please refer to this image of an oxygen outlet:

30f. How many oxygen outlets are there per bed?

_____

(See image above for reference. The color of the oxygen outlet may differ in your country/region.)

31f. What oxygen source is the piping connected to?

☐ PSA system
☐ Liquid tank system
☐ Manifold (distribution ramp)
(PSA=Pressure Swing Adsorption. Check all that apply.)

For the following question, please refer to this image of an oxygen plant:

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32f. What is the PSA system configuration?	◯ Single oxygen generator plants ◯ Duplex oxygen generator plants ◯ Triplex oxygen generator plants ◯ Other (Single generator plants will have a single configuration including only one booster and set of tanks, as in the photo depicted. Duplex generator plants will have two configurations in parallel, including two boosters and set of tanks. These configurations may join at an air compressor junction. Triplex generator plants will have three configurations in parallel, including three boosters and set of tanks. These configurations may join at an air compressor junction.)
33f. Other PSA system configuration:	_____
34f. What is the oxygen production capacity of the PSA system?	_____ (If applicable, write the production capacity of each oxygen generator plant, separated with a semicolon (;). Write number[s] without units.)
35f. Indicate if the oxygen production capacity is recorded in metres cubes/hour(m3/hr) or litres/minute(L/min):	◯ metres cubed/hour (m3/hr) ◯ litres/minute (L/min)
36f. What is the quantity of liquid oxygen contracted for the facility per month?	_____ (Write in whole numbers without units.)
37f. Indicate if the quantity of liquid oxygen is recorded in tons/month, metres cubed(m3)/month, or litres/month:	◯ tons/month ◯ metres cubed (m3)/month ◯ litres/month
38f. Is the PSA plant active 24 hours per day and 7 days per week?	◯ Yes ◯ No (Passive Swing Adsorption (PSA) - generation of enriched oxygenation from ambient air)
39f. How many days per week does the PSA plant function?	_____ (Write number of days without unit label.)
40f. How many hours per day does the PSA plant function?	_____ (Write in number of hours without unit label.)

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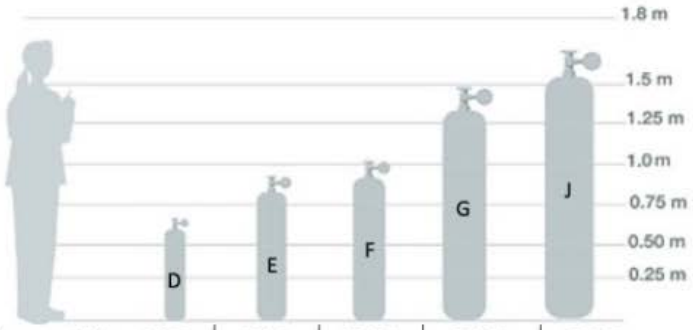
For the following questions, please refer to this image of sizes of oxygen cylinders.



Nominal content [L]:	**340 L**	**680 L**	**1360 L**	**3400 L**	**6800 L**
Height x diameter [mm]:	535 x 102	865 x 102	930 x 140	1320 x 178	1520 x 229
Nominal content [m^3]:	0.34 m^3	0.68 m^3	1.36 m^3	3.4 m^3	6.8 m^3
Water capacity [L]:	2.3 L	4.7 L	9.4 L	23.6 L	47.2 L

WHO-UNICEF technical specifications and guidance for oxygen therapy devices:
https://www.who.int/medical_devices/publications/tech_specs_oxygen_therapy_devices/en/

41**f.** What is the monthly consumption of 340 litre cylinders?

_____ (See above image for reference. Enter number of cylinders. Example: 4. If you do not have this cylinder size, write 0.)

42**f.** What is the monthly consumption of 680 litre cylinders?

_____ (See above image for reference. Enter number of cylinders. Example: 4)

43**f.** What is the monthly consumption of 1360 litre cylinders?

_____ (See above image for reference. Enter number of cylinders. Example: 4)

44**f.** What is the monthly consumption of 3400 litre cylinders?

_____ (See above image for reference. Enter number of cylinders. Example: 4)

45**f.** What is the monthly consumption of 6800 litre cylinders?

_____ (See above image for reference. Enter number of cylinders. Example: 4)

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Annex 4. Statistical Analysis Plan

Statistical analysis plan

Oxygen requirements and approaches to respiratory support in patients with COVID-19 in low- and middle-income countries:
a WHO study

VERSION 2.5
7 December 2022

Contents

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Version control

Version	Approval date	Important changes from previous version	Initials
1.0	15 September 2021	Initial version	SDR
1.1	24 January 2022	Include more states in the multistate model and sample size recalculation	SDR
2.0	23 February 2022	Recalculate sample size and harmonize objectives with research protocol version 5.2, 20 February 2022	SDR
2.2	6 July 2022	Include the scenario of facility level variables as confounders	SDR
2.3	27 October 2022	Recalculate sample size including percentage ICU beds as covariate and correcting GPower input parameters. Include power analysis. Added the two Cox proportional hazard models (patient level and facility level characteristics)	MR
2.4	25 November 2022	Adjust figures according to suggestions made by copyeditor	MR
2.5	7 December 2022	Final technical edit	PR

Notes: Sara Domínguez Rodríguez (SDR): Lead biostatistician (September 2021 – July 2022)
Matthieu Rolland (MR): Lead biostatistician (July 2022 – present)
Pryanka Relan: Global study focal point (2020 – present)

Abbreviations

BiPAP	bilevel positive airway pressure
CI	confidence interval
COVID-19	SARS-CoV-2 coronavirus disease
CPAP	continuous positive airway pressure
DSMB	Data and Safety Monitoring Board
FiO_2	fraction of inspired oxygen
HFNC	high-flow nasal cannula
HR	hazard ratio
ICU	intensive care unit
IMV	invasive mechanical ventilation
IQR	interquartile range
LMICs	low- and middle-income countries
LPM	litres per minute
LR	logistic regressions
NIPPV	non-invasive positive pressure ventilation
NIV	non-invasive ventilation
OR	odds ratio
PEEP	positive end-expiratory pressure
RR	respiratory rate
SAP	statistical analysis plan
SD	standard deviation
SpO_2	peripheral oxygenation saturation

1. Introduction

Plan objective

This statistical analysis plan (SAP) provides a detailed and comprehensive description of the main, pre-planned analysis for the study "Oxygen requirements and approaches to respiratory support in patients with COVID-19 in low- and middle-income countries: a WHO study". This study has been undertaken by an international research consortium and is fully described in the research protocol version 5.2, 20 February 2022.

This SAP contains a detailed description of data summaries and presentations of statistical results. Major changes in the statistical methodology used for the main and pre-planned analyses would, however, require amendment and re-approval of this SAP by the research consortium and study Data and Safety Monitoring Board (DSMB) or a detailed description and justification in the statistical analysis report.

Study characteristics

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as the cause of a respiratory illness, officially named COVID-19. COVID-19 was described as a pandemic on 11 March 2020.

It is estimated that approximately 20% of those infected with COVID-19 require oxygen supportive therapy. Oxygen is an essential medicine and has been listed as such on the WHO Essential Medicines List and Essential Medicines List for Children. Still, the availability of supplemental medical oxygen in low- and middle-income countries (LMICs) remains a challenge. The COVID-19 pandemic has highlighted, more than ever, the acute need for scale-up of oxygen therapy. WHO has provided an inventory tool to quantify facility-level provision of infrastructure to deliver oxygen therapy. Detailed data on the use of oxygen therapy in LMICs at the patient level remain lacking.

In February 2020, the Research and Development Blueprint for COVID-19 identified key research areas needed for understanding this new disease. Clinical research, including that specifically on the types of respiratory support required by patients, was identified as a key research priority. Since mid 2020, the WHO COVID-19 Clinical Characterization and Management Research Group has been developing two research protocols to support the understanding of respiratory support practices and oxygen requirements for the clinical management of COVID-19.

- The first is an observational study to describe oxygen requirements and respiratory support practices in facilities caring for patients with COVID-19 in LMICs.
- The second is an interventional platform trial which seeks to compare modalities of respiratory support (e.g. continuous positive airway pressure [CPAP], high-flow nasal cannula [HFNC], awake prone position, and other interventions?).

Selection of the most relevant interventions requires an understanding of current practice and expertise in sites that might recruit patients to the trial. Existing studies collect data on oxygen mode of delivery but do not characterize the type, quantity and duration of each modality's use at the patient level, to give a better understanding of oxygen therapy modalities in current use in LMICs.

2. Objectives of the analysis

Overall aim of the study

To describe oxygen use, requirements and respiratory support interventions at the facility level in LMICs. This information will be used to further inform a future platform trial of respiratory support strategies.

Primary objectives

Objective 1.1

Characterize the type and duration of different modalities of oxygen therapy and respiratory support delivered to patients with severe and critical COVID-19.

Objective 1.2

To quantify the duration of stay in, describe practice patterns and transition probabilities across, modes of respiratory support, distinguishing absence, nasal or facial, HFNC, invasive mechanical ventilation (IMV), with death and discharge from hospital as absorbing states.

Secondary objectives

Objective 2.1

To quantify the amount (m^3) of oxygen delivered to patients with severe and critical COVID-19.

Objective 2.2

To describe the demographics and outcomes at hospital discharge of this cohort of hospitalized patients. For this, we will collect minimal demographic information (age, sex, chronic disease and pregnancy), daily oxygen saturation (SpO_2) and respiratory rate (RR), and outcome data at hospital discharge.

Objective 2.3

To describe the resources at the facility level for oxygen delivery and respiratory support. For this, we will collect basic facility-level information about oxygen production, distribution and biomedical equipment availability using the WHO Biomedical Inventory Tool.

Objective 2.4

To describe the impact of facility resources on outcome at hospital discharge. For this, we will collect facility-level information on: electricity, biomedical staff, clinical staff who can manage respiratory failure.

3. Endpoints

Study endpoints for primary objectives

- Total number of patients receiving respiratory support daily and proportion of patients receiving various delivery devices: nasal cannula, face mask, Venturi, non-rebreather, HFNC, CPAP, bilevel positive airway pressure (BiPAP), non-invasive ventilation (NIV), IMV (Objective 1.1).
- The proportion of patients with each of the respiratory supports over the 7 days of follow-up, with subgroup analysis by disease severity, and associations between facility type or patient characteristics (Objective 1.2).

Study endpoints for secondary objectives

- Quantification of total oxygen delivered will be estimated by daily oxygen use for each patient from data collected on flow rates, the fraction of inspired oxygen (FiO_2), positive end-expiratory pressure (PEEP) (Objective 2.1).

- Quantification of total oxygen supply among the 7 days of follow-up stratified by type of device (low-flow oxygen therapy, HFNC, NIV/CPAP and IMV), and region (African, Americas, South-East Asia, European, Eastern Mediterranean and Western Pacific) (Objective 2.1).
- Demographics and outcome characteristics at hospital discharge (Objective 2.2).
- Facility-level information about oxygen production, distribution, biomedical equipment availability (Objective 2.3) and electricity, biomedical staff and clinical staff who can manage respiratory failure (Objective 2.4).

4. Statistical methods for specific objectives

Primary objectives

Summary descriptive

In order to describe the study sample, baseline characteristics and output overall, columns will be included to summarize all subjects within the study (Objective 1.1). In summary tables of continuous variables, interquartile ranges (IQR) and medians will be assessed. In summary tables of categorical variables, counts and percentages will be used. The denominator for each percentage will be the number of subjects within the population group excluding missing observations unless otherwise specified. See **Table 1** and **Table 2** for descriptions of admission characteristics. Chi-squared and Fisher Tests will be performed for categorical variables. For normally distributed continuous variables, the Student T-test will be performed and non-parametric tests such as U-Mann Whitney or Kruskal Wallis when non-normally distributed. All hypothesis testing will be carried out at the 5% significance level and *P* values will be rounded to three decimal places. In summary tables, *P* values less than 0.001 will be reported as < 0.001 as implemented in compareGroups R package *(1).*

Respiratory support transitions

To describe the changes in respiratory support over time (Objective 1.2), Sankey plots will be used to describe patient trajectories, describing the proportion and duration of each type of respiratory support. Kaplan-Meier models will be used to estimate the

probability of each transition during the follow-up time of the study. The hospital outcomes and time to event outcomes will be described in **Table 3**.

A multistate model will be used to study the course of hospital stay of the study population. The focus of the analysis will be on evaluating transitions of escalating respiratory support and transitions to the absorbing states. Multistate models are structures that represent different disease categories or states and the movement of patients between these states (transitions). In this model, summarized in **Fig. 1**, patients may enter the study in one of the three initial transient states: State A: No oxygen therapy or standard oxygen therapy (nasal cannula, face mask or non-rebreather mask); State B: HFNC, NIV or CPAP; and State C: IMV. The model will also include two absorbing states from which a patient no longer transitions: discharge alive and recover (State D) and dead (State E). From State A, a patient can either transition to State B (HFNC/NIV/CPAP), State C (IMV), discharge/recover, or die. From State B (HFNC/NIV/CPAP), a patient can transition into IMV, discharge, or die. From State C (IMV), a patient can transition to discharge/recover or die. Formally the course of a patient's stay is described with a time-in homogeneous Markov chain given by $\{X(t), t \geq 0\}$ with finite state space $S = \{1, 2, 3, 4, 5, 6, 7, 8, 9\}$ and follow-up time τ. $X(t)$ denotes the state occupied at time t. Various estimands are of interest. We will define the probability to move from one state to another within the multistate model. To perform this multistate model, the *mstate* R package*(2)* will be used to estimate the transition and state occupation probabilities for patients over the course of their hospital stay. The *mstate* package employs Aalen-Johansen estimator based on Markov assumptions.

A multivariable regression model will be used to predict each transition based on the following characteristics: age, gender, vaccination and comorbidities at the time of hospital admission, SpO_2 on the day of the transition, the percentage of intensive care unit (ICU) beds in the facility, and a random intercept at the facility level. The output of the multistate model will be summarized using a forest plot as in **Fig. 2** describing the hazard ratios (HR) and 95% of confidence interval (CI) for each baseline covariate in each transition. Stacked transition probabilities at 7 days after admission will be plotted.

Secondary objectives

The amount of oxygen used for each patient will be computed using the following formula:

- For nasal cannula, face mask and non-rebreather mask, FiO_2 is assumed to be 1.0 and flow rates are adjustable in litres per minute (LPM). Litres per day consumption of oxygen = device flow rate L/minute x 60 minutes/hr x 24 hr/day.

- For HFNC FiO_2 is adjustable (defaulted to 1.0) and flow rate is adjustable in LPM. Litres per day consumption of oxygen = device flow rate L/minute x 60 minutes/hr x 24 hr/day; flow rate in LPM = device flow rate x (FiO_2 - 0.21)/0.79.
- For ventilator, CPAP, BiPAP/non-invasive positive pressure ventilation (NIPPV), FiO_2 is adjustable (defaulted to 1.0) and flow rate is adjustable in LPM and dependent on multiple factors. Liter per day consumption of oxygen = device oxygen consumption rate L/minute x 60 minutes/hr x 24 hr/day. Device oxygen consumption rate in LPM = (minute ventilation + (bias flow x RR x expiratory time/60) + leak) x (FiO_2 - 0.21)/0.79.

This amount of oxygen used for each patient will then be summarized according to oxygen modality, severity and region, as in **Fig. 3**. Different panels will be displayed for box plots summarizing medians and IQR. Comparisons between each stratum will be done using the Kruskal Wallis test (Objective 2.1). Baseline characteristics and overall output columns will be included to summarize all subjects at discharge. In summary tables of continuous variables, IQR and medians will be assessed. In summary tables of categorical variables, counts and percentages will be used. The denominator for each percentage will be the number of subjects within the population group without taking into account missing observations unless otherwise specified. Chi-squared and Fisher Tests will be performed for categorical variables. For normally distributed continuous variables, the Student T-test will be performed and U-Mann Whitney or Kruskal Wallis when non-parametric. All hypothesis testing will be carried out at the 5% significance level and *P* values will be rounded to three decimal places (Objective 2.2). An additional multivariate Cox proportional hazard model will be performed where the outcome is time to death, and the covariates are age, gender, vaccination, comorbidities and SpO_2 at the time of hospital admission, the percentage of ICU beds in the facility, and a random intercept at the facility level. All these covariates will be included in the model and no variable selection process will be performed, as these covariates were all identified as being clinically relevant (Objective 2.2). To describe the oxygen source, distribution, biomedical equipment and oxygen capacity at the facility level, data will be displayed as a whole and summarized by each region and level of facility (Objective 2.3). See **Table 4** for descriptions of oxygen supply at each facility. In summary tables, *P* values less than 0.001 will be reported as < 0.001, as implemented in compareGroups R package *(1).* To assess the impact of facility-level resources, a multivariate Cox proportional hazard model will be performed where the outcome is time to death, and where the covariates will include: electricity, biomedical staff and clinical staff who can manage respiratory failure. All these covariates will be included

in the model and no variable selection process will be performed, as these covariates were all identified as being clinically relevant (Objective 2.4).

Fig. 1. Multistate model

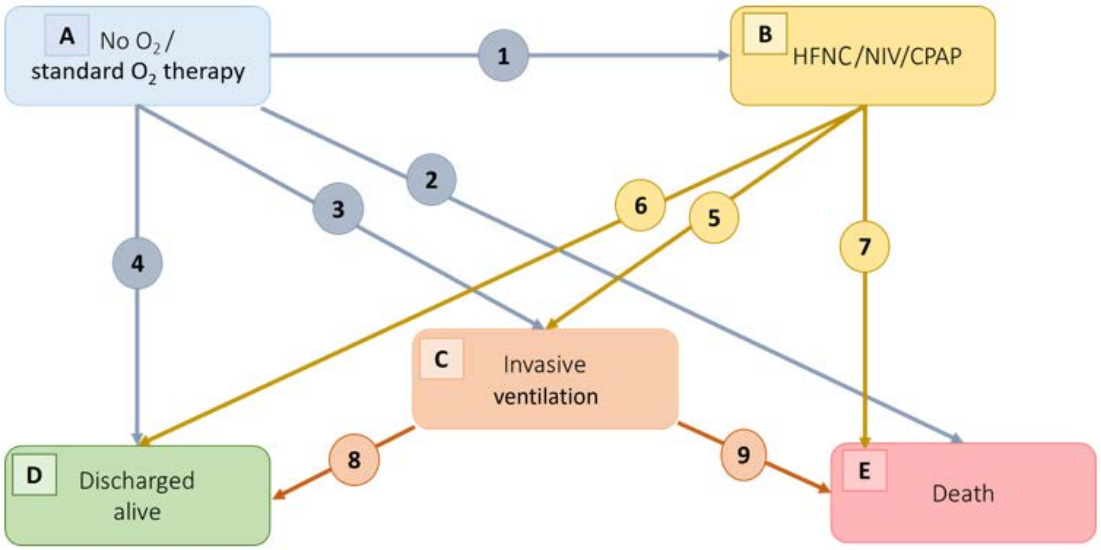


Fig. 2. Output from the multistate model

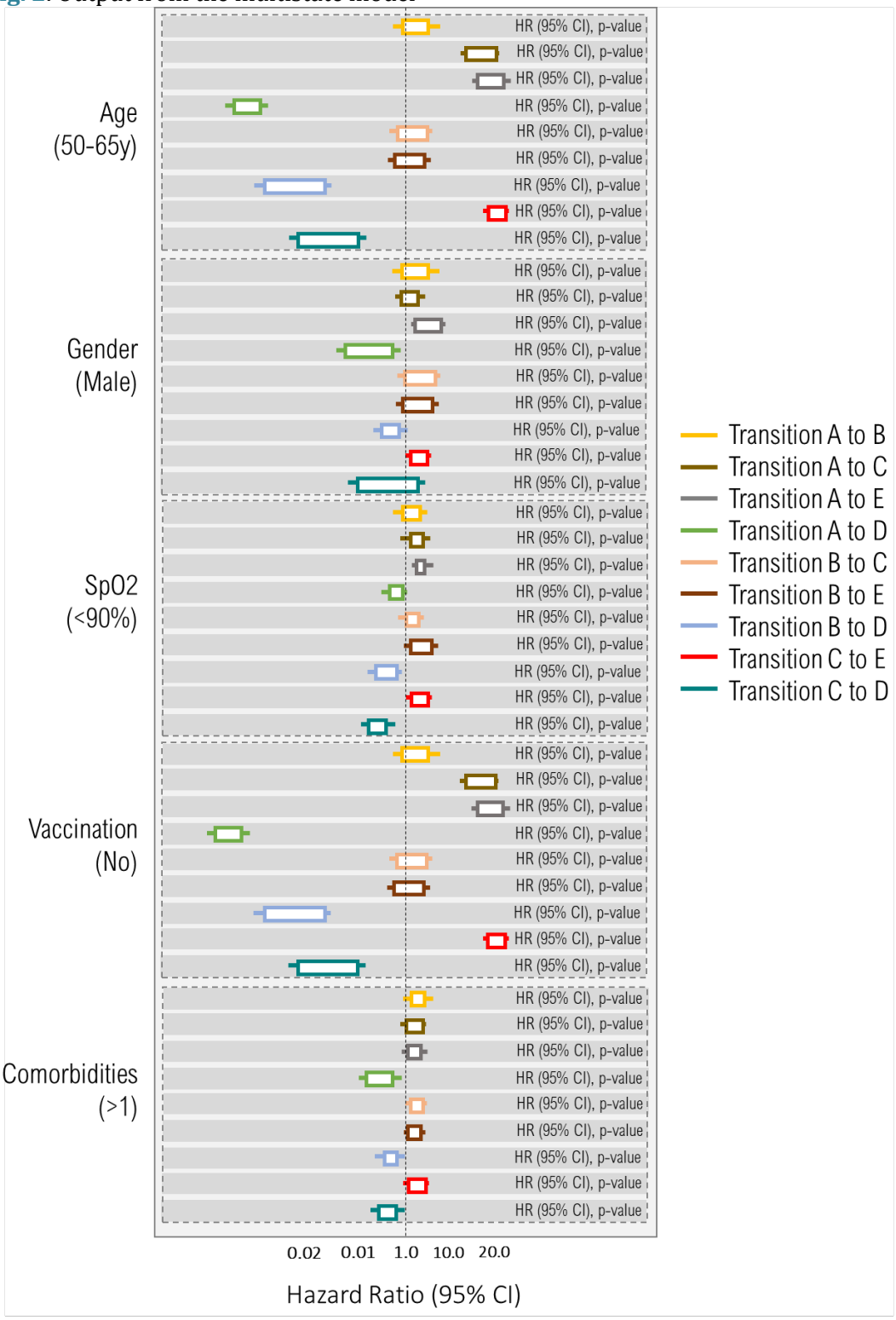


Fig. 3. Amount of oxygen according to oxygen modality, severity and region

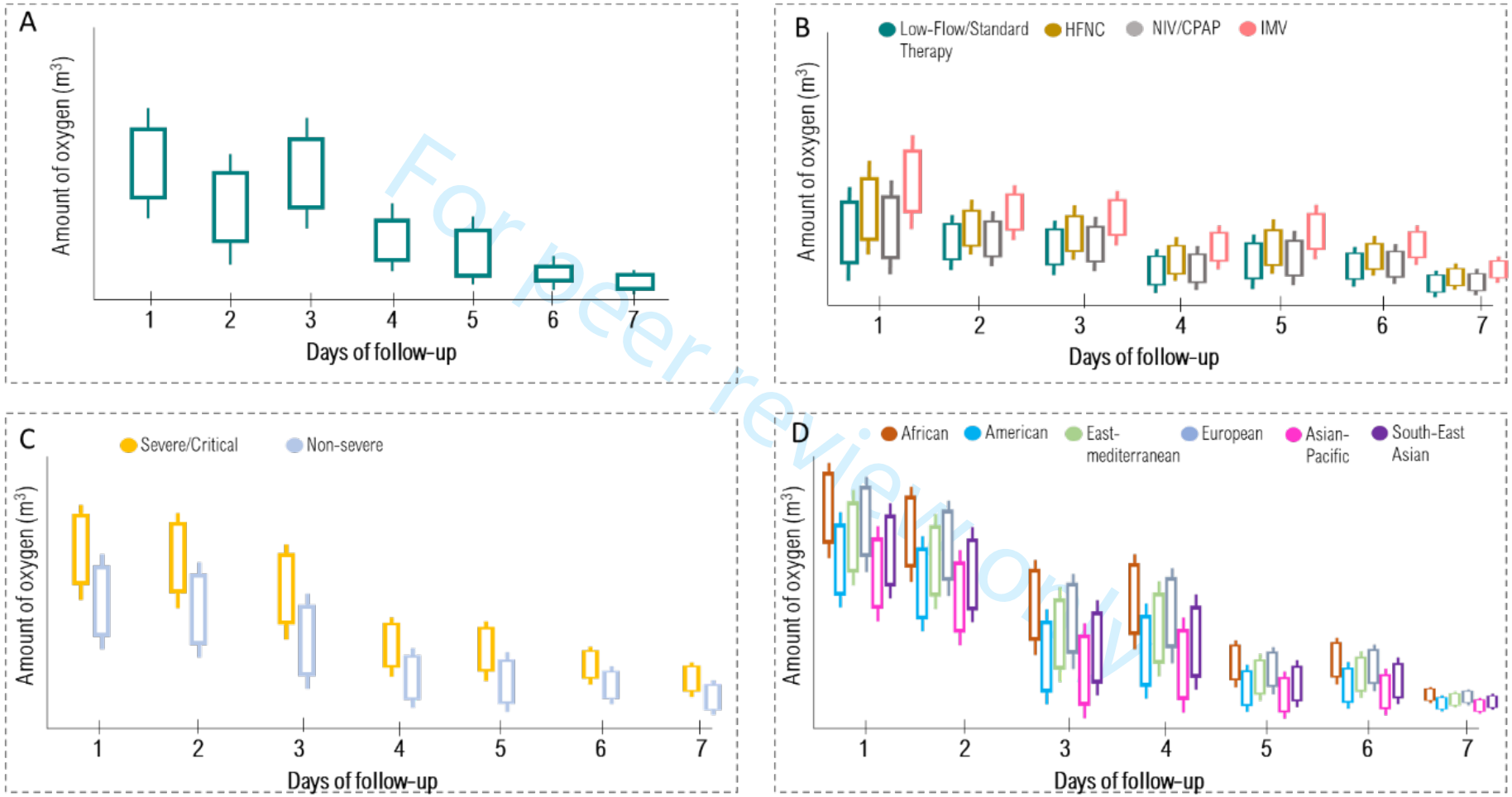


Table 1. Characteristics at admission

Variable	Overall N =
Age	
Years (median, IQR)	
13–17 years	
18 –49 years	
50–69 years	
≥ 70 years	
Gender	
Female (n, %)	
Pregnancy status	
Yes (n,%)	
Admission vital signs	
Heart rate bt/min (median, IQR)	
> 100 bt/min (n, %)	
> 120 bt/min (n, %)	
Respiratory rate b/min (median, IQR)	
> 20 breaths/min (n,%) (adults)	
> 40 breaths/min (n, %) (children)	
Blood pressure mmHg (median, IQR)	
> 140 mmHg (n, %) (adults)	
Oxygen saturation (median, IQR)	
< 90% (n, %)	
< 94% (n, %)	
Mental status	
Alert (n, %)	
Verbal (n, %)	
Pain (n, %)	
Unresponsive scale (AVPU) (n, %)	
Height (cm)	
Weight (kg)	
Body mass index (BMI)	
< 18.5 (n, %)	
> 30 (n, %)	
> 40 (n, %)	
Chronic conditions	
None (n, %)	
Chronic cardiac disease (n, %)	
Hypertension (n, %)	
Chronic obstructive pulmonary disease (n, %)	
Asthma (n, %)	
Chronic liver disease (n, %)	
Dementia (n, %)	
Chronic neurological disease (n, %)	
Human immunodeficiency virus (HIV) (n, %)	
Not on ART (n, %)	
Diabetes (n, %)	
Current smoking (n, %)	
Tuberculosis (n, %)	
Asplenia (n, %)	
Cancer (n, %)	
Pathogen testing at any time during hospitalization	
Variant Alpha (n, %)	
Variant Beta (n, %)	
Variant Gamma (n, %)	
Variant Delta (n, %)	
Variant Omicron (n, %)	
Other	
Unknown (n, %)	
Vaccination status	
Vaccinated (n, %)	

Table 2. Respiratory support at hospitalization

Variable	Overall N =
Respiratory and critical care interventions	
Prone position	
Prone (n, %)	
Sitting (fowlers) (n, %)	
Semi-fowlers (n, %)	
Lateral (n, %)	
Lying flat on back (n, %)	
Oxygen therapy	
Flow	
1–5 LPM (n, %)	
6–10 LPM (n, %)	
11–15 LPM (n, %)	
> 15 LPM (n, %)	
Fraction of inspiring oxygen (%)	
Median [IQR]	
Peal airway pressure (cm)	
Median [IQR]	
Positive end-expiratory pressure (cm)	
Median [IQR]	
Respiratory rate (breaths/min)	
Median [IQR]	
Source of oxygen	
Cylinder (n, %)	
Concentrator (n, %)	
Piped/wall oxygen (n, %)	
Other (n, %)	
Oxygen therapy modality	
Room air (n, %)	
Nasal cannula (n,%)	
Simple face mask (n, %)	
Venturi mask (n, %)	
Non-rebreather mask (n, %)	
HFNC (n, %)	
CPAP (n, %)	
Bubble (n, %)	
Nasal pillows (n, %)	
Helmet (n, %)	
Full face mask (n, %)	
BiPAP (n, %)	
Full face mask (n, %)	
Nasal pillows (n, %)	
Helmet (n, %)	
Invasive mechanical ventilation (n, %)	
Other (n, %)	
Ventilator mode	
Volume control (n, %)	
Pressure control (n, %)	
Synchronized intermittent mandatory ventilation (n, %)	
Pressure support (n, %)	
Other (n, %)	

Table 3. Outcomes at hospital discharge

Variable	Overall N =
Hospital outcomes	
Clinical status at discharge	
Death (n, %)	
Alive – clinical improved (n, %)	
Alive – not clinical improved (n, %)	
Lost (n, %)	
Oxygen requirements on discharge	
Yes (n, %)	
Source	
Cylinder (n, %)	
Concentrator (n, %)	
Other (n, %)	
Delivery devices	
Nasal cannula (n, %)	
Simple face mask (n, %)	
Venturi mask (n, %)	
Non-breather mask (n, %)	
CPAP/BiPAP (n, %)	
Other (n, %)	
Patients discharged with pulse oximeter (n, %)	
Time to event outcomes	
Length of hospital stay	
Days from hospital admission until transfer or death	
Days of hospitalization of survivors	
Days of hospitalization of non-survivors	

Table 4. Oxygen supply at each facility

Variable	Overall N =	African Region N =	Region of the Americas N =	South-East Asia Region N =	European Region N =	Eastern Mediterranean Region N =	Western Pacific Region N =
Total beds available							
Median (IQR)							
Total ICU beds available							
Median (IQR)							
Staff dedicated for maintenance of medical equipment							
Yes (n, %)							
Number of staff (n, %)							
Total number of ventilators							
Median (IQR)							
Total number of BiPAP							
Median (IQR)							
Total number of CPAP							
Median (IQR)							
Total number of HFNC							
Median (IQR)							
Back-up generator							
Yes (n, %)							
Grid electricity collection							
Yes (n, %)							
Piped network for medical gases							
Yes (n, %)							
Bedside concentrators							
Yes (n, %)							
Number median (IQR)							
Oxygen cylinders							
Yes (n, %)							
Quantity used monthly							
Liquid oxygen capacity							
Yes (n, %)							
Pressure swing adsorption plant							
Yes (n, %)							

5. Missing data

Records with missing admission dates will be excluded from the analysis. To avoid loss of information and statistical power in the association analysis, missing data will be imputed using a non-parametric random forest imputation algorithm implemented in the missForest R package *(3)*. To prevent too many assumptions, only variables with less than 10% of missing information will be considered for imputation. To get a better understanding of the way missing data distribute among variables in the study, correlation matrixes, patching patterns, and box plot analyses will be performed by means of several functions implemented in MICE and VIM R packages. By checking the missing pattern distribution, missing data would be considered either non-completely at random, missing not at random, or missing at random. Sensitivity analyses on complete cases will be performed.

6. Sample size

The sample sizes to assess associations between each transition and patient's characteristics at the time of hospital admission were calculated.

Because there exists no published method to perform power analysis for multistate models, a priori power analysis was calculated for separate logistic regressions (LR) corresponding to each of the transitions of interest presented in Fig. 1. For each of these LRs, the event of interest was the probability for a patient to go through the transition during their hospitalization. Basal transition rates between states were hypothesized by the Study Steering Committee WHO panel of experts in the reference population, and are summarized in Fig. 4. Basal event rates (Pr Y=1) were derived from these transition rates as summarized in Table 5. Seven covariates were considered (age, gender, vaccination, SpO2, having at least one comorbidity, having more than one comorbidity, and the percentage ICU beds in the facility). A priori distributions for these covariates were estimated using the WHO Global Clinical Platform, as summarized in Table 6. The sample size was estimated to achieve in a two-sided z-test with a α=0.01 to account for the multiple testing incurred, and a power of at least 0.9. The squared multiple correlations for covariates were estimated in a moderate R2=0.2 using the procedure of Demidenko with variance correction (4). G*Power 3.1 Software was used for the estimations (5). No literature was found to estimate odds ratios (ORs) for the percentage ICU beds indicator so sample size was computed for a conservative OR = 2 for each of the transitions.

Table 6 displays the sample size required to estimate the effect of each of age, gender, vaccination, SpO_2, presence of comorbidities and percentage ICU beds on each transition under these assumptions. A chart provided in Fig. 5 shows the achieved power for a given sample size. Table 7 displays the sample size required to estimate the effect of each of the facility level characteristics in the facility level model: electricity availability, number of biomedical experts and number of health care workers who provide direct patient care and can manage patients with respiratory failure on the time to death under these assumptions. A chart provided in Fig. 6 shows the achieved power for a given sample size for this last model. G*Power input parameters are available upon request. The proposed multivariable analysis sample size is N = 1378.

World Health Organization

Fig. 4. The estimated rate of transitions

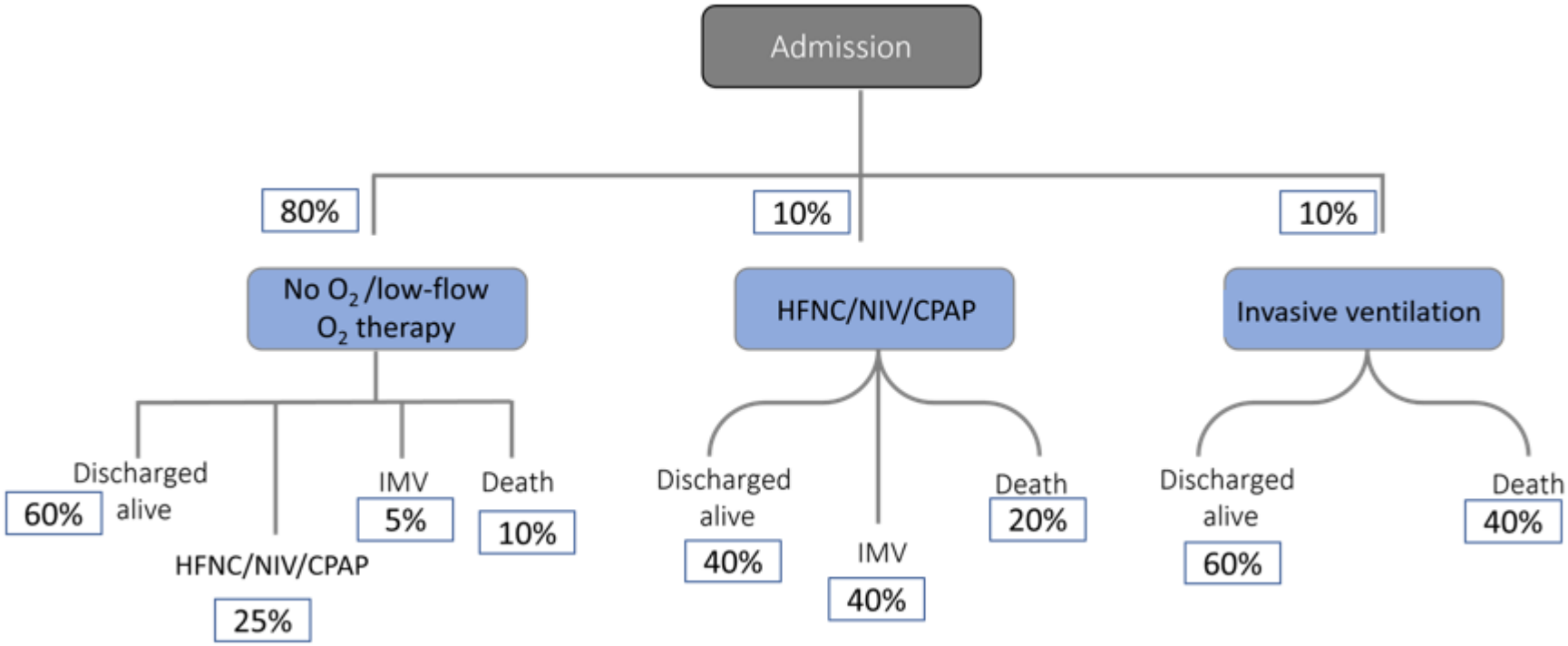


Table 5. Computation of basal event rates based on transition rates described in Fig. 4; the total proportion of admitted patients that will pass through the transition from state A to state B

Transition number in Fig. 1	State A	State B	Among admitted patients, percent to go through state A[a]	Among patients in state A, percent to transition to state B[b]	Basal event rate[c]
1	No O_2/standard O_2 therapy	Non-invasive ventilation	80%	25%	**20.0%**
2	No O_2/standard O_2 therapy	Death	80%	10%	**8.0%**
3	No O_2/standard O_2 therapy	Invasive ventilation	80%	5%	**4.0%**
5	Non-invasive ventilation	Invasive ventilation	30%	40%	**12.0%**
7	Non-invasive ventilation	Death	30%	20%	**6.0%**
9	Invasive ventilation	Death	26%	40%	**10.4%**

[a] Sum of patients to go through a given state, irrespective of their trajectory.
[b] See Fig. 4.
[c] Among all admitted patients, proportion to go through transition A → B = p(A) * p(B).

Table 6. A priori distribution parameters for covariates to be included in the model, necessary for sample size computation

Covariate	Estimated distribution in study population[a]
50–65 year olds	28%
Male	47%
Vaccinated	21%
SPO_2 < 90%	22%
1 comorbidity	28%
> 1 comorbidity	24%

[a] Estimation derived from the WHO Global Clinical Platform.

Table 7. Sample size estimation for each covariate in the multivariable analysis to assess the association with each transition

Probability of transition from No O_2/standard O_2 therapy to HFNC/NIV/CPAP			Reference	Sample size*
	reference	Interest		
Age	*18–29 years old*	*50–65 years old* **4 times higher**	CDC, July 19 2021 *(8)*	N = 227
Gender	*Male*	**3 times higher**	https://www.nature.com/articles/s41467-020-19741-6	N = 309
Vaccination	*No*	**Yes 12 times higher**	https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html#covidnet-hospitalizations-vaccination	N = 96
SpO_2	*> 90%*	*< 89%* **4 times higher**	Mejía F et al., 2021 *(9)*	N = 264
Comorbidity (1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 369
Comorbidity (> 1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 405
% ICU beds	*Continuous*	*+/- 1 SD* **OR = 2**	No literature	N = 265
Probability of transition from No O_2/standard O_2 therapy to death				
Age	*18–29 years old*	*50–65 years old* **35 times higher**	CDC, July 19 2021 *(8)*	N = 51
Gender	*Female*	**3 times higher**	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8270145/	N = 572
Vaccination	*No*	**14 times higher**	https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html#rates-by-vaccine-status	N = 101
SpO_2	*> 90%*	*< 89%* **4 times higher**	Mejía F et al., 2021 *(9)*	N = 436
Comorbidity *(1)*	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 660
Comorbidity (> 1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 720

% ICU beds	*Continuous*	*+/- 1 SD* **OR = 2**	No literature	N = 496
Probability of transition from No O_2/standard O_2 therapy to IMV				
Age	*18–29 years old*	*50 –65 years old* **35 times higher**	CDC, July 19 2021 *(8)*	N = 67
Gender	*Male*	**3 times higher**	https://www.nature.com/articles/s41467-020-19741-6	N = 1038
Vaccination	*No*	**12 times higher**	https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html#covidnet-hospitalizations-vaccination	N = 174
SpO_2	*> 90%*	*< 89%* **4 times higher**	Mejía F et al., 2021 *(9)*	N = 758
Comorbidity (1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 1182
Comorbidity (> 1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 1285
% ICU beds	*Continuous*	*+/- 1 SD* **OR = 2**	No literature	N = 880
Probability of transition from HFNC/NIV/CPAP to IMV				
Age	*18–29 years old*	*50–65 years old* **4 times higher**	CDC, July 19 2021 *(8)*	N = 290
Gender	*Male*	**3 times higher**	https://www.nature.com/articles/s41467-020-19741-6	N = 421
Vaccination	*No*	**12 times higher**	https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html#covidnet-hospitalizations-vaccination	N = 99
SpO_2	*> 90%*	*< 89%* **4 times higher**	Mejía F et al., 2021 *(9)*	N = 334
Comorbidity (1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 492
Comorbidity (> 1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 538

% ICU beds	*continuous*	*+/- 1 SD* **OR = 2**	No literature	N = 367
Probability of transition from HFNC/NIV/CPAP to death				
Age	*18–29 years old*	*50–65 years old* **35 times higher**	CDC, July 19 2021 *(8)*	N = 55
Gender	*Male*	**3 times higher**	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8270145/	N = 726
Vaccination	*No*	**14 times higher**	https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html#rates-by-vaccine-status	N = 116
SpO_2	*> 90%*	*< 89%* **4 times higher**	Mejía F et al., 2021 *(9)*	N = 542
Comorbidity (1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 833
Comorbidity (> 1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 907
% ICU beds	*Continuous*	*+/- 1 SD* **OR = 2**	No literature	N = 624
Probability of transition from IMV to death				
Age	*18–29 years old*	*50–65 years old* **35 times higher**	CDC, July 19 2021 *(8)*	N = 49
Gender	*Male*	**3 times higher**	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8270145/	N = 467
Vaccination	*No*	**14 times higher**	https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html#rates-by-vaccine-status	N = 92
SpO_2	*> 90%*	*< 89%* **4 times higher**	Mejía F et al., 2021 *(9)*	N = 365
Comorbidity (1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 543
Comorbidity (> 1)	*No*	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 593
% ICU beds	*Continuous*	*+/- 1 SD* **OR = 2**	No literature	N = 407

Fig. 5. Achieved power vs sample size for the multistate model

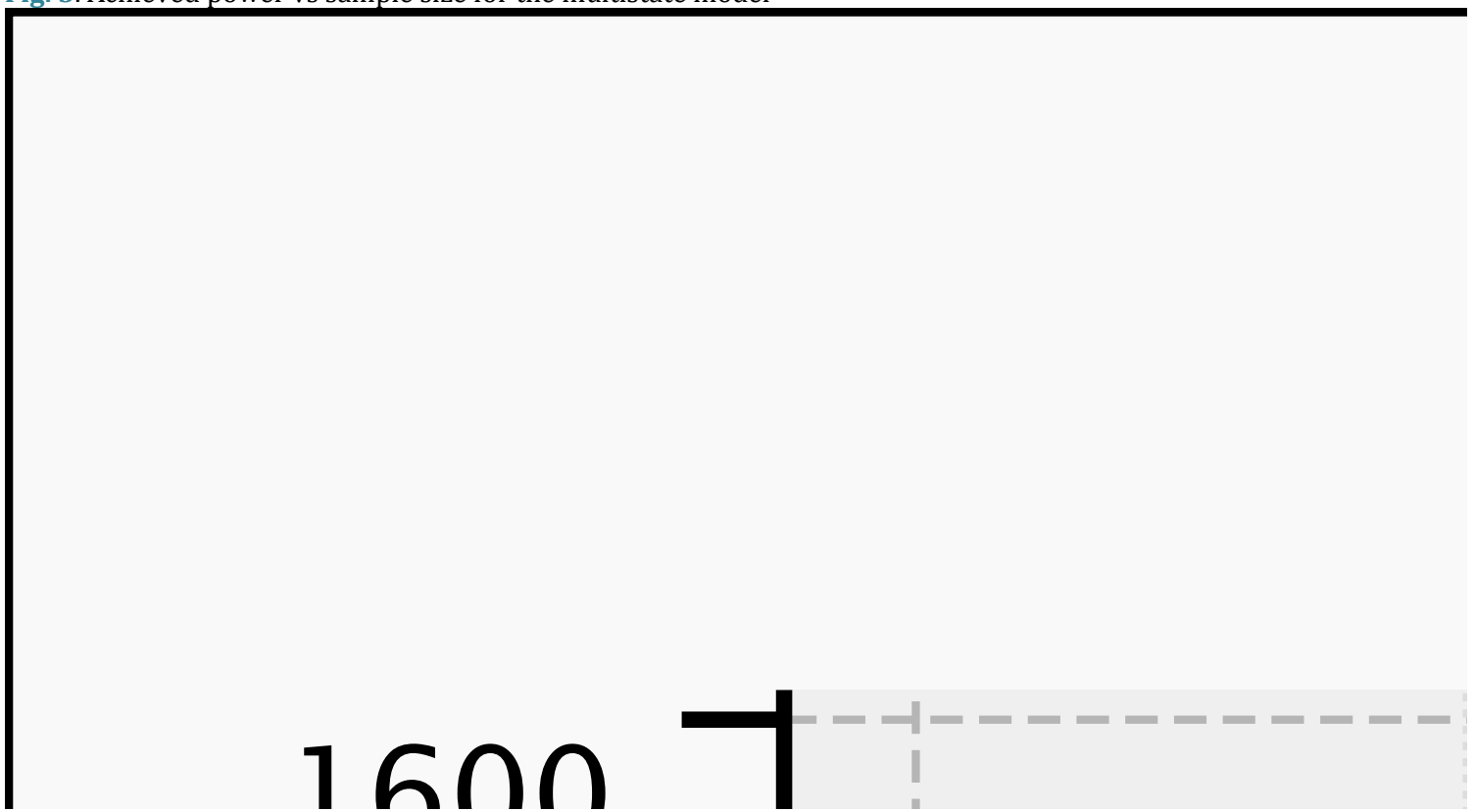
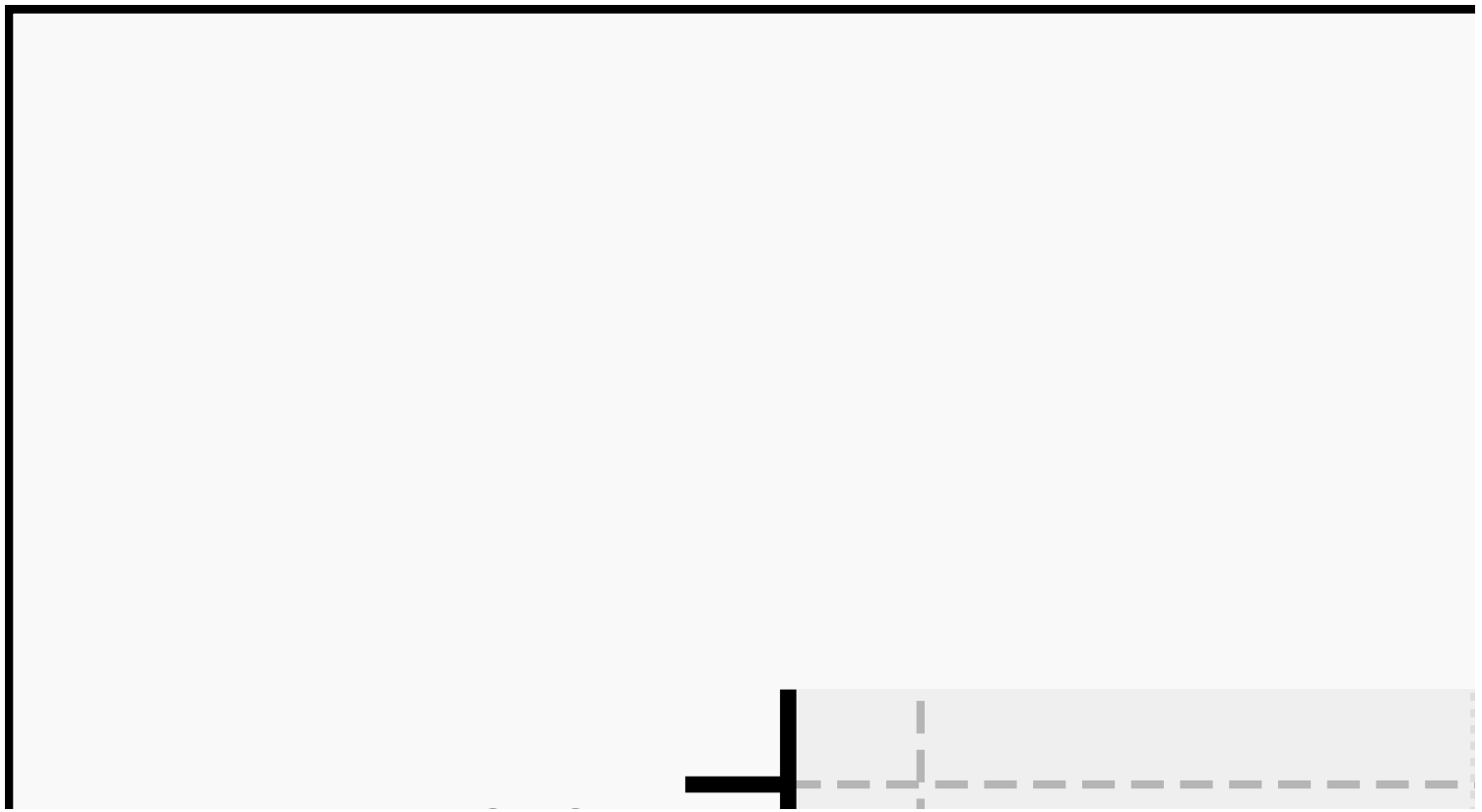


Table 8. Sample size estimation for each covariate in the multivariable analysis to assess the association with death

	Probability of death		Reference	Sample size
	Reference	Interest		
Electricity	*No* 5% event rate	*Yes* **5 times higher**		N = 634
Biomedical staff	*> 90%* 5% event rate	*< 89%* **4 times higher**	Mejía F et al., 2020 *(9)*	N = 852
Any clinical staff who can manage respiratory failure	*No* 5% event rate	*Yes* **3 times higher**	Zhou Y et al., 2020 *(10)*	N = 1378

Fig. 6. Achieved power vs sample size for the facility level model



7. Statistical software

All analyses will be conducted in R (*R: a language and environment for statistical computing*. R Core Team, R Foundation for Statistical Computing, Vienna, Austria; 2020 (https://www.R-project.org) *(7).*

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Annex 5. Data sharing agreement

DATA-SHARING AGREEMENT

Schedule of particulars

This Data-Sharing Agreement is comprised of: (i) this Schedule of Particulars; (ii) Annex I – General Conditions; and (iii) Annex II – Project Description (together, the "**Agreement**").

Pursuant to the terms of this Agreement, the Contributor hereby agrees to provide, and WHO hereby agrees to accept, the Data for the Purpose of Use and subject to the Restrictions on Use.

In this Agreement, the following expressions have the following meanings:

1. The " **Contributor**": [full legal name of your institution];
2. "**WHO**": the World Health Organization, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland;
3. The "**Data**": Any data, results and reports, unpublished or otherwise, collected during or resulting from the Project which are owned by the Contributor and provided by the Contributor to WHO during the term of this Agreement;
4. The "**Parties**": the Contributor and WHO;
5. The "**Project**" as further described in Annex II;
6. The "**Purpose of Use**": The Data are provided to WHO for WHO to implement the Project which is summarized in Annex II and for use in related materials and activities, including but not limited to WHO's internal research purposes;
7. The "**Restrictions on Use**": The Data shall not be used for any purpose other than the Purpose of Use;
8. The "**Term of Agreement**": [Unrestricted in time]; and
9. "**Data Charges**": The Data will be provided free of charge.

Acknowledged and agreed:

Signed for and on behalf of WHO		Signed for and on behalf of the Contributor
Name:	Janet Diaz	Name:
Title:	Lead, Clinical Management for COVID-19	Title:
Date:		Date:

DATA-SHARING AGREEMENT

Annex I – General Conditions

1. Use

1.1. The Data are supplied by the Contributor to WHO solely for the Purpose of Use and subject to the Restrictions on Use.

1.2. Other than for and within the Purpose of Use, the Data shall not be transferred, sold, offered for sale or otherwise used, without the prior written agreement of the Contributor.

1.3. WHO shall only allow parties who have a need to know for the Purpose of Use and who are bound by similar obligations of confidentiality and restrictions on use as contained in this Agreement to have access to the Data.

1.4. In implementing the Purpose of Use, WHO will: not attempt to identify or contact research participants included in the Data; Respect the confidentiality of the Data; and maintain the Data in a secure location on a password-protected, WHO-internal network protected by standard encoding and the WHO firewall for the duration of the Purpose of Use.

2. Confidentiality

2.1. The Data may incorporate confidential information of the Contributor. Accordingly, if and to the extent any such Data are clearly marked by the Contributor as "confidential", WHO shall during the term of this Agreement and for a period of five years following its termination, treat such Data confidential and only disclose them under like obligations of confidentiality and restrictions on use as those contained herein. WHO shall be deemed to have fulfilled its obligations, if it exercises at least the same degree of care in maintaining confidentiality as it would in protecting its own confidential information.

2.2. However, the above mentioned obligations of confidentiality shall not apply to Data which:
(i) can be shown to have been known to WHO at the time of its acquisition from the Contributor; (ii) are acquired from a third party, not in breach of any obligation of confidentiality to the Contributor; (iii) are independently devised or arrived at by, on behalf of, or for WHO without access to the Information; or (iv) enter the public domain otherwise than by breach of the undertakings set out in this Agreement.

3. Rights

3.1. Except for the rights explicitly granted to WHO hereunder, nothing contained in this Agreement shall be construed as conveying any rights under any patents or other intellectual property which either party may have or may hereafter obtain.

3.2. Nothing contained in this Agreement shall restrict the Contributor's right to sell, transfer, assign or distribute the Data to any other person for commercial or non-commercial purposes.

4. Publications

4.1. Subject to the Contributor's proprietary rights, the results obtained through use of the Data within the Purpose of Use may be published by WHO and/or parties collaborating with WHO. In order to avoid prejudice to the Contributor's proprietary rights, WHO shall transmit any material intended to be published or relevant portions thereof, to the Contributor under confidential cover for review at least ten days prior to its submission to any editor, publisher, referee or meeting organizer. In absence of any objection by

the Contributor within that thirty-day period concerning prejudice to its proprietary rights, the publication may proceed, provided, however, that the Contributor shall be duly acknowledged in such publication.

4.2. WHO will prepare manuscript(s) of the results of the Purpose of Use for publication, pursuant to the terms of the applicable protocol, and publish such manuscripts pursuant to WHO's rules and regulations, including its policy on open access, as contained at: http://www.who.int/about/policy/en/. WHO may further use the results of the Purpose of Use to update relevant WHO recommendations and develop any guidelines, including publication thereof, and may further publish those results.

4.3. If a manuscript of the Research Activities is submitted for publication, WHO will in all events retain the Data until the peer review process is completed, and then for one year after publication to ensure sufficient time to address any required responses to the findings (e.g., letters to the editor).

4.4. WHO will ensure that all publications relating to the Data will appropriately acknowledge WHO, the Contributor, and all other entities contributing data to the publication.

5. Undertakings of the Contributor

5.1. The Contributor represents and warrants that: It has obtained all rights and permissions necessary to transfer the Data to WHO and for WHO to implement the Purpose of Use and all other activities relating to the Data as described herein; The Data have been collected from clinical trials, observational studies, or surveillance systems that have been conducted in accordance with all applicable laws.

5.2. Prior to transmitting the Data to WHO, the Contributor will: Verify whether approval from their local/relevant Ethics Review Committee is required for the use of the Data for the Purpose of Use, and if that approval is required, obtain it; and Anonymize all participant-level data in the Data, pursuant to agreed standards, to remove all information in the Data that could be used to identify research participants.

5.3. The Contributor will transmit the Data to WHO securely, using secure file transfer protocol.

5.4. The Contributor will avoid providing to WHO any information relating to the Data or the Research Activities that relates to a natural person, which, either directly or indirectly, in combination with other information available or likely to be available to WHO, can identify such natural person.

5.5. The Contributor makes no warranty of the fitness of the Data for any particular purpose or any other warranty, either express or implied. However, to the best of the Contributor's knowledge, the use of the Data within the Purpose of Use shall not infringe on the proprietary rights of any third party.

5.6. WHO agrees that (except as may explicitly be provided in this Agreement) the Contributor has no control over the use that is made of the Data by WHO or parties collaborating with WHO in accordance with the terms of this Agreement. Consequently, WHO agrees that the Contributor shall not be liable for such use.

6. Other Matters

6.1. Nothing in this Agreement shall be interpreted as establishing a partnership between the parties or establishing one party as the agent of the other or conferring a right on one party to bind the other, except as may be specifically set out herein.

6.2. Without the prior written approval of the other Party, neither Party shall, in any statement or material of an advertising or promotional nature, refer to this Agreement or the relationship between the Parties, or use the name (or any abbreviation thereof) and/or emblem of the other Party.

6.3. Any dispute relating to the interpretation or application of this Agreement shall, unless amicably settled, be subject to conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the parties or, in the absence of agreement, with the rules of arbitration of the International Chamber of Commerce. The Parties shall accept the arbitral award as final.

6.4. Nothing contained herein shall be construed as a waiver of any of the privileges and immunities enjoyed by WHO under national or international law and/or as submitting WHO to any national court or jurisdiction.

6.5. This Agreement sets forth the entire understanding between the parties and supersedes any prior agreements, written or verbal related to the Data. It shall only be capable of change by written amendment executed by duly authorized officers of the Parties.

DATA-SHARING AGREEMENT

Annex II – Project Description

Oxygen requirements and approaches to respiratory support in patients with COVID-19 in low- and middle-income countries: an observational study.

Background: The COVID-19 pandemic has highlighted, more than ever, the acute need for scale up of oxygen therapy. WHO has provided an inventory tool to quantify facility-level provision of infrastructure to deliver oxygen therapy. However, data on the use of oxygen therapy at the patient-level remains lacking.

Population studied: Suspected or confirmed COVID-19 patients receiving oxygen therapy.

Study design: We propose to conduct an observational study of patients with suspected or confirmed COVID-19 receiving oxygen therapy. Basic information and risk factor information will be collected from participants. Participants will be followed for 7 days or until outcome (hospital discharge or death).

Outcomes and analyses: Determination of the person-time on specific respiratory modalities (nasal cannula, face mask, Venturi, NRB, HFNC, CPAP, BiPAP, invasive mechanical ventilation); Proportion of patients on each respiratory modality; Facility oxygen supply metrics; Outcome of patient as measured by WHO clinical progression scale, censored at 30 days.

Please refer to the specific protocol and relevant documents (questionnaire, health care facility questionnaire). For questions contact: covidrespstudy@who.int

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	1

Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	#4	Present key elements of study design early in the paper	4-5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for	7

		for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	6-7
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6-7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	6-7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	
Statistical methods	#12c	Explain how missing data were addressed	6
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	
Statistical methods	#12e	Describe any sensitivity analyses	6
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for	N/a – will be done for results, this is a protocol

		for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	N/a – will be done for results, this is a protocol
Participants	#13c	Consider use of a flow diagram N/a – will be done for results, this is a protocol	
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	N/a – will be done for results, this is a protocol
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest N/a – will be done for results, this is a protocol	
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount) N/a – will be done for results, this is a	

protocol			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
N/a – will be done for results, this is a protocol			
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/a – will be done for results, this is a protocol
Main results	#16b	Report category boundaries when continuous variables were categorized	N/a – will be done for results, this is a protocol
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
N/a – will be done for results, this is a protocol			
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	

Discussion			
Key results	#18	Summarise key results with reference to study objectives	N/a – will be done for results, this is a protocol
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	N/a – will be done for results, this is a protocol
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	N/a – will be done for results, this is a protocol
Generalisability	#21	Discuss the generalisability (external validity) of the study results	6
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11