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

Annexes

Contents

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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.

Annex 3. Case report form

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Respiratory support observational study - Screening/Recruitment
Page 1

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.)

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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.)
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.)

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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.

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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

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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

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"

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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

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.)

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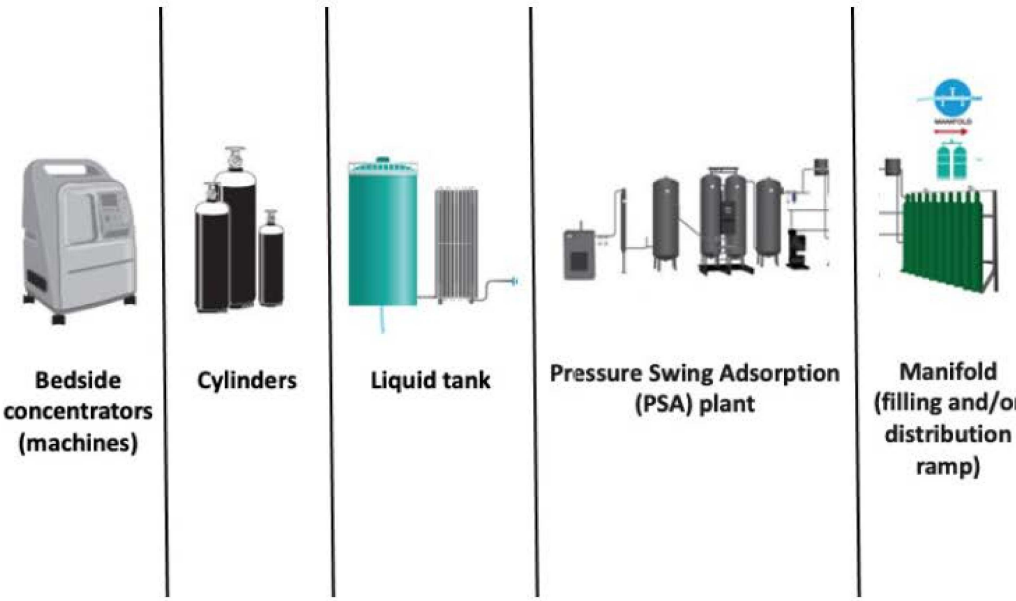
For the following questions, please refer to this image of oxygen supply types.



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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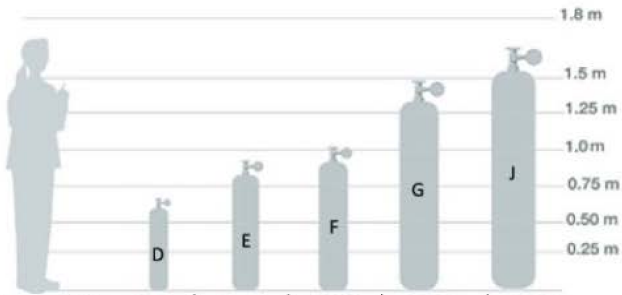
32f. What is the PSA system configuration?	◯ Single oxygen generator plants ◯ Duplex oxygen generator plants ◯ Triplex oxygen generator plants ◯ Other (Single generator plants will have a single configuration including only one booster and set of tanks, as in the photo depicted. Duplex generator plants 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.)

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 [m³]:	0.34 m³	0.68 m³	1.36 m³	3.4 m³	6.8 m³
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)

World Health Organization

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

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

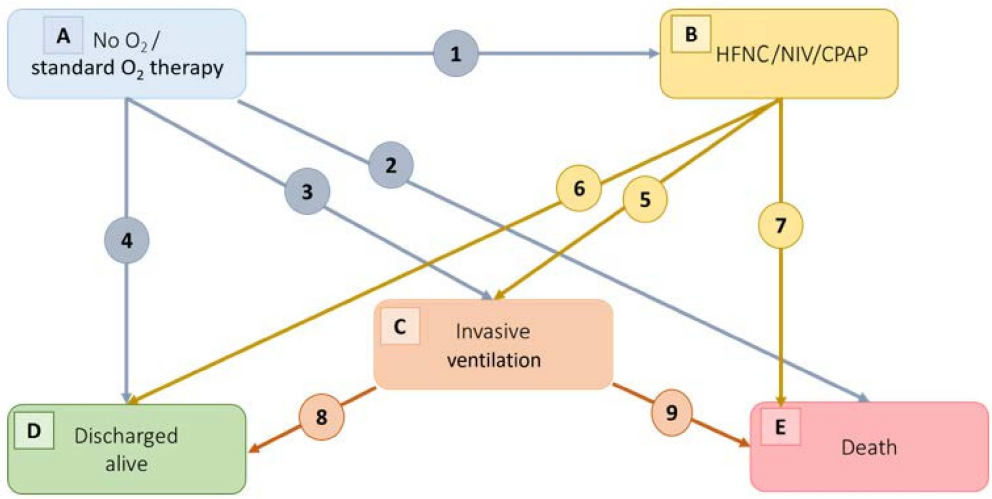


Fig. 2. Output from the multistate model

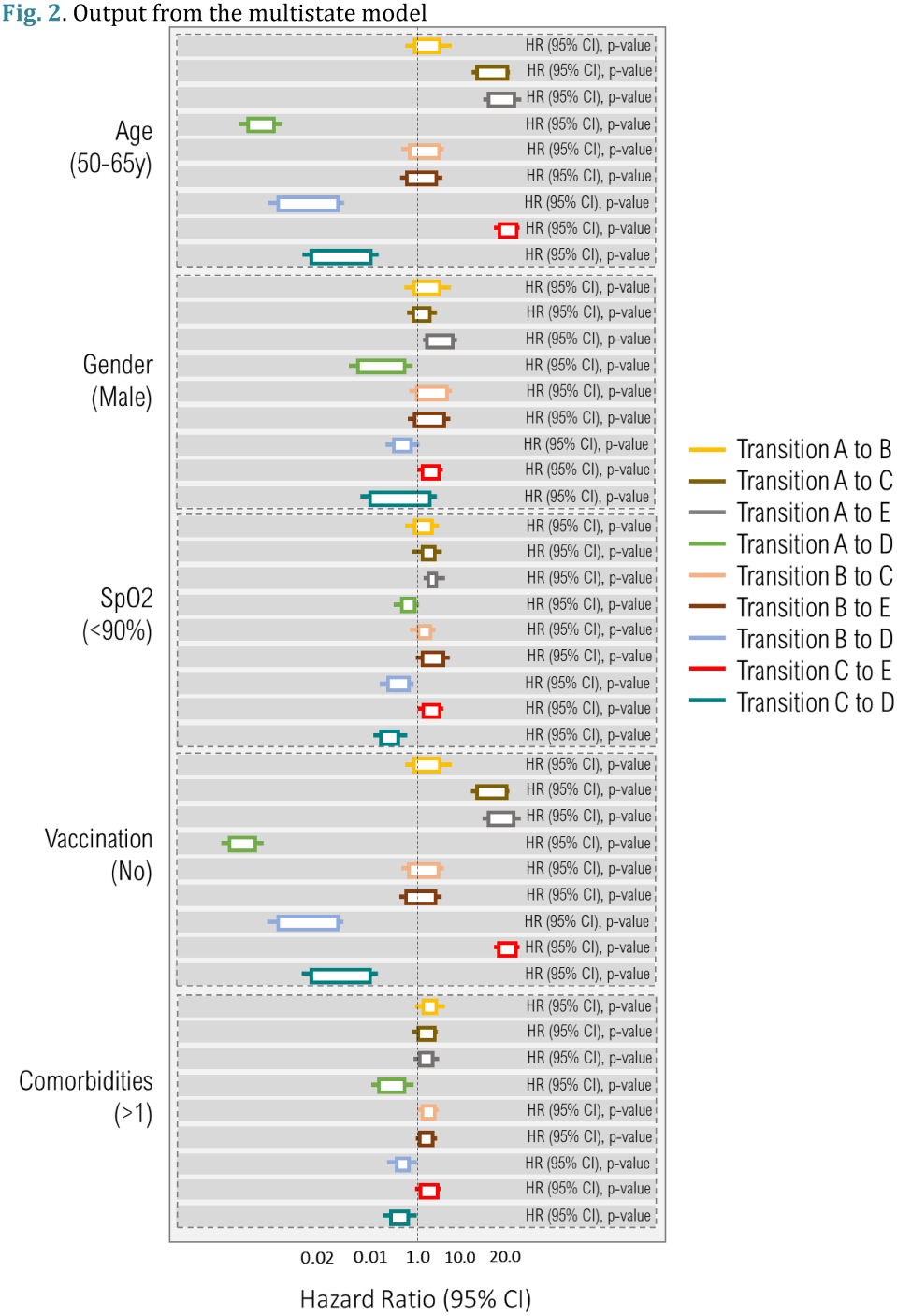


Fig. 3. Amount of oxygen according to oxygen modality, severity and region

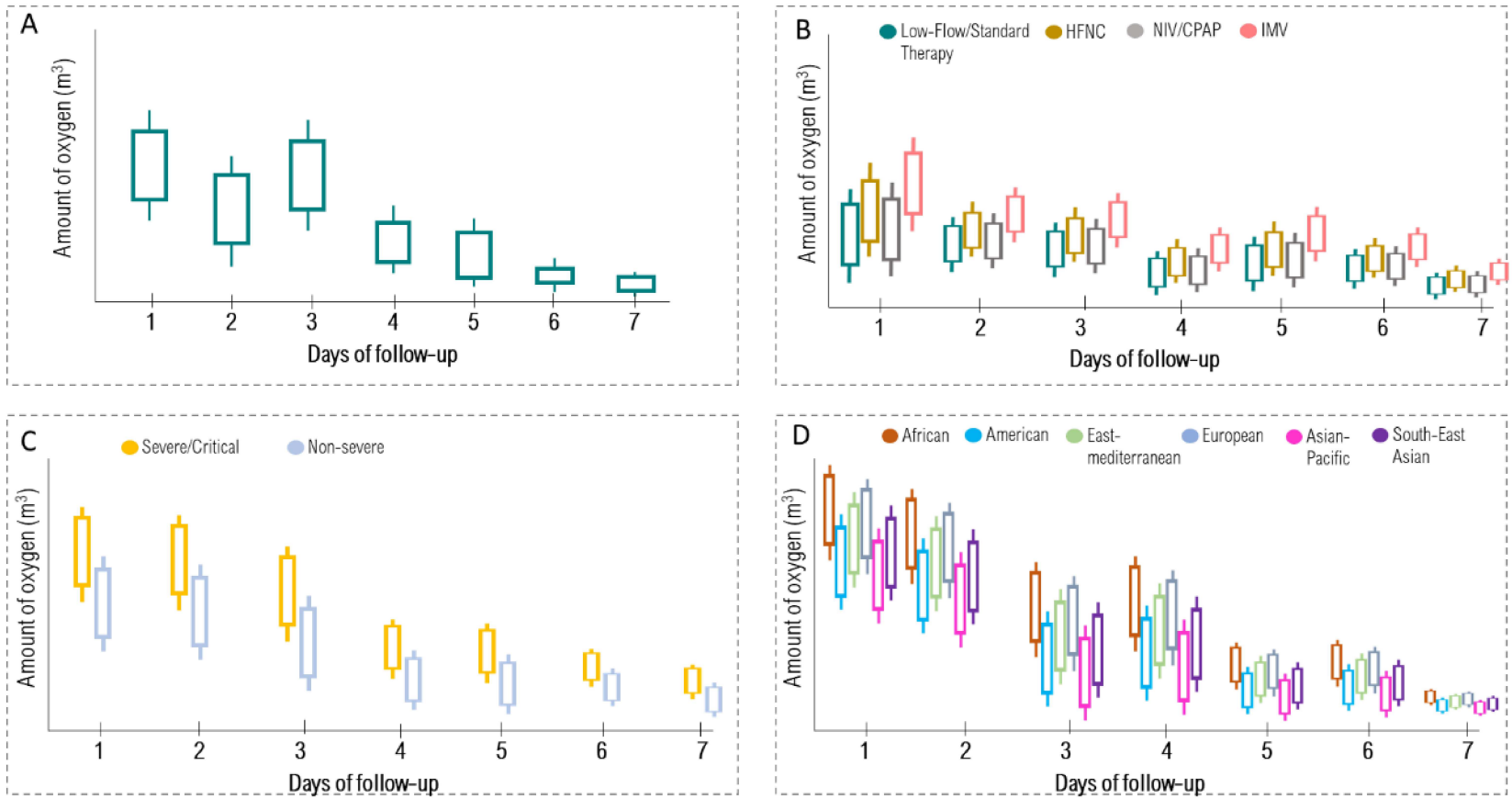


Table 1. Characteristics at admission

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.

Fig. 4. The estimated rate of transitions

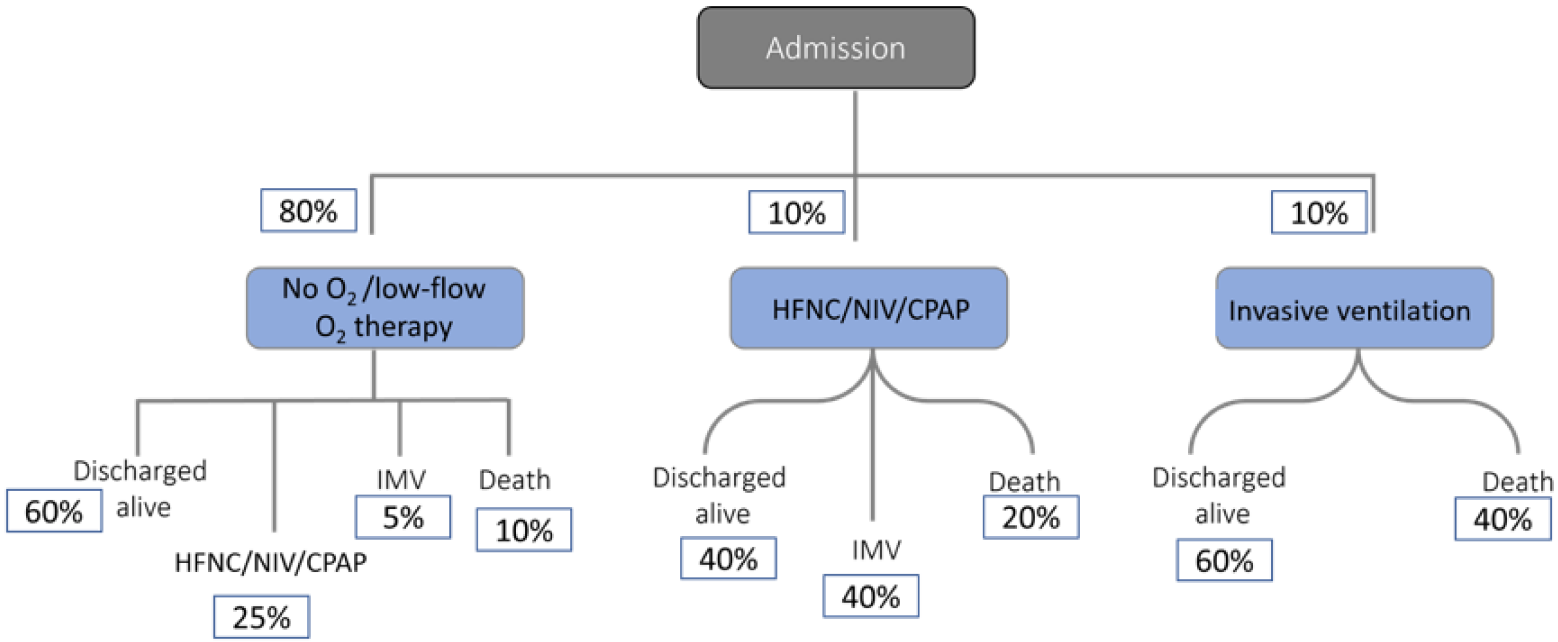


Table 5. Computation of basal event rates based on transition rates described in Fig. 4; the total proportion of admitted patients that will pass through the transition from state A to state B

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

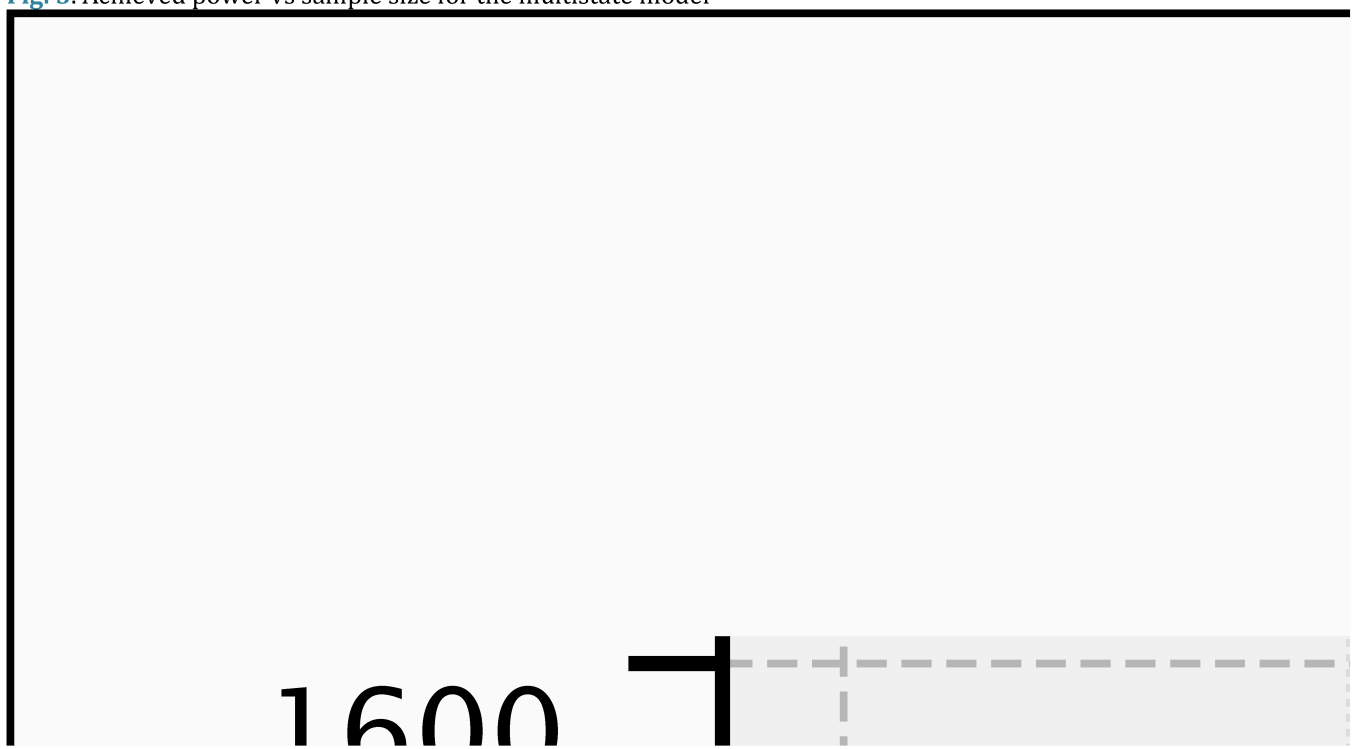
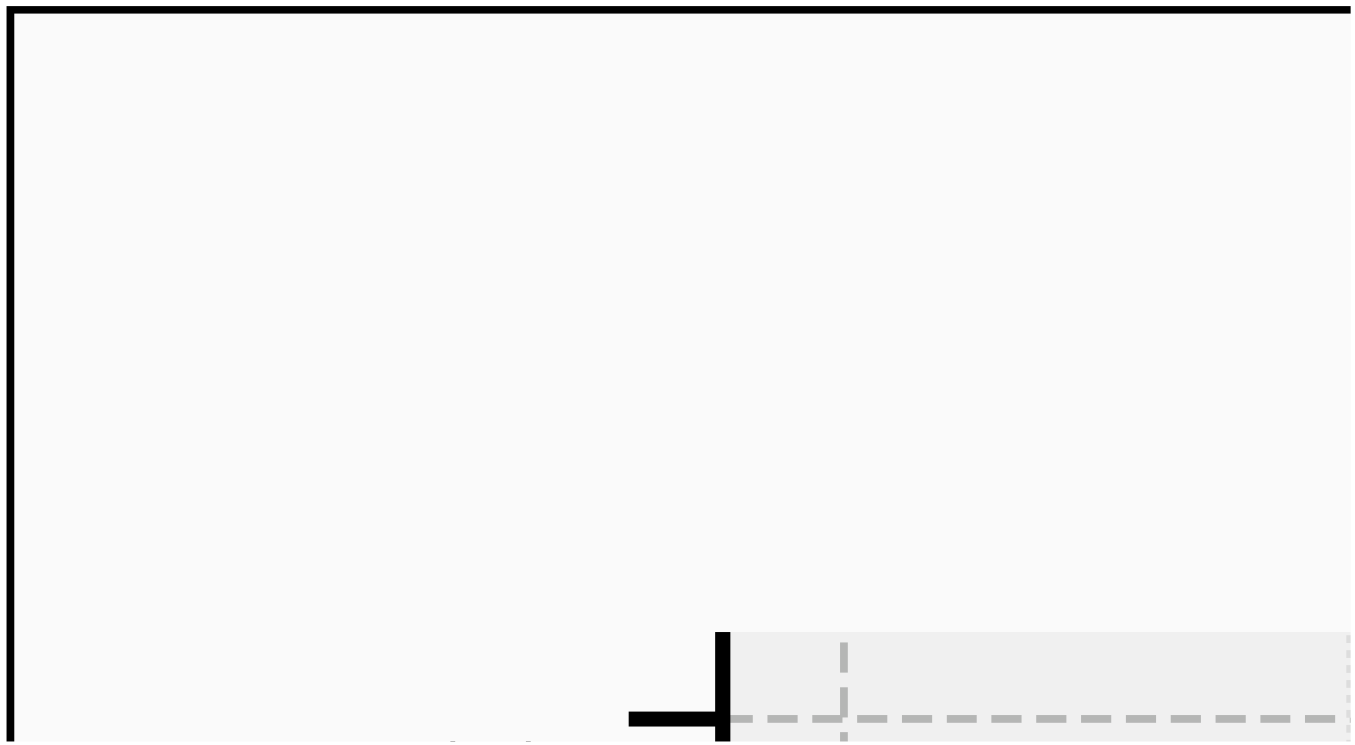


Table 8. Sample size estimation for each covariate in the multivariable analysis to assess the association with death

	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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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:

Relan P, *et al. BMJ Open* 2023; 13:e071346. doi: 10.1136/bmjopen-2022-071346

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