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WHO O2CoV2: oxygen requirements and respiratory support in patients with COVID-19 in low-and-middle income countries—protocol for a multicountry, prospective, observational cohort study

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ABSTRACT

Introduction SARS-CoV-2 has been identified as the cause of the disease officially named COVID-19, primarily a respiratory illness. COVID-19 was characterised 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 Model List of 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 low-and-middle income countries at the patient and facility level are needed to target interventions better globally.

Methods and analysis We aim to describe the requirements and use of oxygen at the facility and patient level of approximately 4500 patients with COVID-19 in 30 countries. Our objectives are specifically to characterise type and duration of different modalities of oxygen therapy delivered to patients; describe demographics and outcomes of hospitalised 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 multistate 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 WHO Ad Hoc COVID-19 Research Ethics Review Committee (ERC) 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.

Trial registration number NCT04918875.

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.

INTRODUCTION

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 characterised 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 WHO Model List of Essential Medicines 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 (LMICs) remain 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 Working 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 characterise 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 Global Health 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) characterise 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 hospitalised 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

Strengthening the Reporting of Observational Studies in Epidemiology (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 LMICs from each of the six WHO regions, and targeting up to four 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 (Gross national income (GNI) per capita of US$12 696 or more in 2020)
UMC	World Bank upper-middle-income economies (GNI per capita of US$4096–US$12 695 in 2020)
LMC	World Bank lower-middle-income economies (GNI per capita of US$1046–US$4095 in 2020)
LIC	World Bank low-income economies (GNI per capita of US$1045 or less in 2020)

Study site selection

To recruit interest in participation, WHO put out a global call for Expressions of Interest (EOIs) 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 website.[12] EOIs were requested to include information about previous experience with WHO and clinical research, research staff, and COVID-19 burden. See online supplemental 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 subregional division prior to site randomisation to have at least one country within each subregion of the continent. Finally, EOIs were randomised 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

- Age greater than or equal to 12 years.
- 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 PCR via nasopharyngeal or oropharyngeal sample or by SARS-CoV-2 antigen detection rapid diagnostic test (Ag-RDT) that meet the minimum performance requirements of ≥80%

sensitivity and ≥97% specificity compared with a nucleic acid amplification test reference assay.
- Admitted to healthcare facility within 24 hours.
- 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 oxygen saturation (SpO_2) ≤90%, SpO_2 <94% if any emergency signs are present.
- 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 online supplemental 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 (online supplemental 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 (CRF) and data entry platform (REDCap) on a WHO-provided tablet computer. See online supplemental 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 oxygen delivery device, 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 generalisation of the results, and thus for descriptive analyses we aim for at least 125 patients per hospital, a maximum total of 4500 patients. For inferential analyses, sample size estimates suggest a minimum of 1380 patients to attain 95% statistical power to achieve hypotheses discussed with the ISSC.

Selection bias

To minimise selection bias, the following are introduced:
- Systematic and randomised site selection procedure (described earlier);
- Specific objective criteria for participant study eligibility (described earlier); and
- Waiver of informed consent (see ethical considerations).

Outcomes

To characterise 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 patients receiving respiratory support daily and proportion of patients receiving various delivery devices: nasal cannula, face mask, Venturi, non-rebreather, hi-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), non-invasive ventilation and 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 as daily oxygen use from data collected on flow rates, fraction of inspired oxygen (FiO_2) and positive end-expiratory pressure.

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, 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×60 minutes/hour×24 hours/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×60 minutes/hour×24 hours/day; flow rate in LPM=device flow rate×(FiO_2−0.21)/0.79.
- For ventilator, CPAP and BiPAP/non-invasive positive pressure ventilation, FiO_2 is adjustable (defaulted to 1.0) and flow rate is adjustable in LPM and dependent on multiple factors. Litres per day consumption of oxygen=device oxygen consumption rate L/minute×60 minutes/hour×24 hours/day. Device oxygen consumption rate in LPM=(minute ventilation+(bias flow×RR×expiratory time/60)+leak)×(FiO_2−0.21)/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 is available in online supplemental annex 4.

Study administration

Data collection and management

Standardised CRFs are available and include:

- Screening form;
- Case identification (ID) 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, which 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 (anonymised and without any patient identifiers) for data analysis, as requested.

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 ID 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 finalise the publication and archival process. The sharing of anonymised data will be done using standard WHO data sharing agreements (see online supplemental annex 5) with each study site.

Study personnel at sites: roles and responsibilities

- Principal investigators at all sites will be responsible for the submission and approval process of protocols to institutions.
- Study investigator teams 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

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

WHO Ad Hoc COVID-19 Research Ethics Review Committee (CERC.0040) has approved this global protocol.

Ethics

WHO Ethics Review Committee (ERC) has determined that this master protocol meets the Council for International Organizations of Medical Sciences 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 stigmatising. Finally, all data are anonymised and linked to patient identity only through a linkage log that will be maintained *securely at study sites.*
- *Four, ERBs 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.* Online supplemental 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, predefined study ID 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 ID 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 anonymised 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 harmonised 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 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.

Data statement

All study forms available in online supplemental annex 3.

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Contributors PR and DA conceived the study and wrote the first draft; PR, JD, SDR and JCM designed the study. SC and SDR developed the statistical analysis plan. YMA, WW-S and PC cochaired 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, YMA, JCM, PC, WW-S, DA and SM approved final version for submission.

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