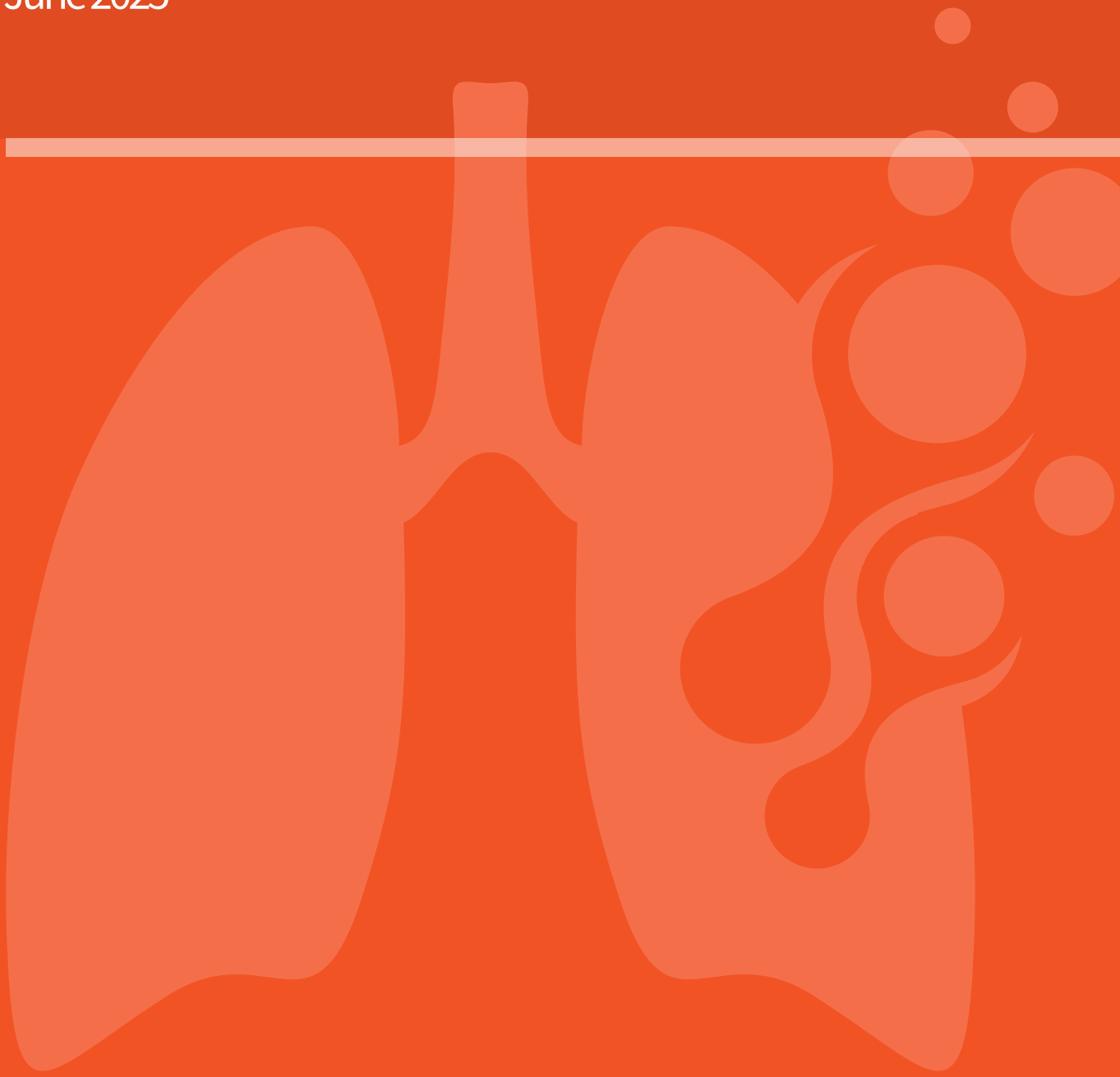
World Health Organization

Clinical management of COVID-19: living guideline

June 2025



Suggested citation. Clinical management of COVID-19: living guideline, June 2025. Geneva: World Health Organization; 2025. https://doi.org/10.2471/B09467. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at https://iris.who.int/.

Contact

Safe and Scalable Care, World Health Organization
Geneva, Switzerland
cmtm@who.int

Contents

SUMMARY

Clinical guideline: What are the interventions to manage patients with COVID-19?

Target audience: People directly or indirectly involved in the health care of patients with COVID-19 and post COVID-19 condition. This includes clinicians, allied health care workers, facility managers and hospital administrators.

New recommendations (v8): There are two new recommendations about the use of antibiotics which follow from recent meta-analysis of outcomes of patients treated with antibiotics for COVID-19. These are:

- For patients with **non-severe** COVID-19 and a low clinical suspicion of a concurrent bacterial infection, we recommend no empirical antibiotics.
- For patients with **severe** COVID-19 and a low clinical suspicion of a concurrent bacterial infection, we suggest no empirical antibiotics.

New structure (v8): These guidelines have evolved from the first version in 2020 in line with new information and changing circumstances of the pandemic. Notable changes to COVID-19 disease over this time have been overall reduced infection rates and reduced disease severity. Emergency measures which were imposed have also been removed, and care for patients with COVID-19 has become more integrated with usual healthcare systems. This different environment has prompted a review of the scope and content of all existing guidance. In order to maintain a clear focus and relevance, we have removed recommendations which would be considered general medical principles, and those which are no longer specific to the management of COVID-19.

Complementary guidelines: For the most up to date clinical practice guideline on therapeutics and COVID-19 see WHO website and BMJ website and MAGICapp.

The guideline creation process:

WHO selected Guideline Development Group (GDG) members providing balanced representation by global region, gender, and technical expertise. Recommendations are created using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. The technical unit collected and managed declarations of interests (DOIs), assessed and acted on competing interests which would prevent participation. No relevant conflicts were identified.

ABBREVIATIONS

ADL	activities of daily living
AGP	aerosol-generating procedure
AHRF	acute hypoxaemic respiratory failure
ARDS	acute respiratory distress syndrome
AWaRe	Access, Watch or Reserve (antibiotics)
BiPAP	bilevel positive airway pressure
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CBT	cognitive behavioural therapy
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CRF	case record form
CT	computed tomography
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
ECMO	extracorporeal membrane oxygenation
EOS	end of study
FiO2	fraction of inspired oxygen
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HFNO	high-flow nasal oxygen
HIV	human immunodeficiency virus
ICU	intensive care unit
IFRC	International Federation of Red Cross and Red Crescent Societies
IMV	invasive mechanical ventilation
IPC	infection prevention and control
IPT	interpersonal therapy
IQR	interquartile range
IVIG	intravenous immune globulin
LMIC	low- and middle-income countries
LOS	length of stay
LRT	lower respiratory tract
LTCF	long-term care facility
MAGIC	Magic Evidence Ecosystem Foundation

MAP	mean arterial pressure
MERS-CoV	Middle East respiratory syndrome coronavirus
MHPSS	mental health and psychosocial support
MIS-C	multisystem inflammatory syndrome in children
NAAT	nucleic acid amplification test
NCD	noncommunicable disease
NICU	neonatal intensive care unit
NIV	non-invasive ventilation
NRSI	non-randomized study of intervention
OI	Oxygenation Index
OSI	Oxygenation Index using SpO2
PaO2	partial pressure arterial oxygen
PBW	predicted body weight
PCC	post COVID-19 condition
PEEP	positive end-expiratory pressure
PEM	post-exertional malaise
PESE	post-exertional symptom exacerbation
PICO	population, intervention, comparator, outcome
PICS	post-intensive care syndrome
PPE	personal protective equipment
PTSD	post-traumatic stress disorder
PUI	person/patient under investigation
QNS	quality assurance of norms and standards
RCT	randomized controlled trial
RDT	rapid diagnostic test
RM	recruitment manoeuvre
RT-PCR	reverse transcription polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus
SBP	systolic blood pressure
SIRS	systemic inflammatory response syndrome
SOFA	sequential organ failure assessment
SOT	standard oxygen therapy
SpO2	oxygen saturation
SR	systematic review
TB	tuberculosis
UNICEF	United Nations Children’s Fund

URT	upper respiratory tract
VoC	variants of concern
VTE	venous thromboembolism
WHO	World Health Organization

1. BACKGROUND

SARS-CoV-2 continues to infect several thousands of people daily leading to preventable morbidity and mortality across the world *(547)*. The roll-out of vaccines and treatment for COVID-19, and increasing population immunity from infection has substantially reduced hospitalization, severity of disease, and mortality. However, the virus continues to evolve in terms of infectivity, immune escape, and disease severity. This guideline robustly and transparently addresses the changing landscape and evidence availability, and the continual development of treatment and management strategies for COVID-19 *(6)*.

Clinical characterization

Asymptomatic infection: Meta-analysis of 94 studies in 2022 suggested that asymptomatic infection represents 32% (95% CI 25.3–39.5%) of all SARS-CoV-2 infection, with 20% (17–25%) of people remaining asymptomatic throughout the course of infection *(561)*. The proportion of cases that are asymptomatic declines with age, which may explain some of the wide variation between cohorts of individuals, and across geographies *(560)*.

Severity classification: Data from 2020 demonstrated that amongst symptomatic patients, most developed only mild (40%) or moderate (40%) disease (see Table 6.3 for definitions), and approximately 15% developed severe disease which requires oxygen support. Critical disease occurred in 5%, with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multi-organ failure, including acute kidney injury and cardiac injury *(13)*. An evaluation from 2022 recorded reduced case fatality rates in 47 out of 50 countries during the Omicron compared with Delta variant periods. Modelling suggested this was attributable to decreased pathogenicity and increased vaccination coverage *(559)*. Individual risk factors represent a strong predictor of severe disease (requiring hospitalization) or death, including male sex, Asian and Black ethnic backgrounds, deprivation, higher body mass index (BMI), and chronic disease *(558)*.

Mental and neurological manifestations: COVID-19 is associated with a spectrum of mental and neurological manifestations, including anxiety, depression, sleep problems, headache, dizziness, impaired sense of smell or taste *(14)*, myalgias, delirium/encephalopathy, agitation, stroke, hypoxic ischaemic brain injury, seizures, coma, meningoencephalitis and Guillain-Barré syndrome *(15)(16)(17)(18)(19)*. Over 80% of COVID-19 patients in a hospitalized United States' cohort experienced neurological symptoms during the course of their illness and these manifestations were associated with a four-fold higher risk of severe COVID-19 *(26)*.

People with pre-existing mental or neurological conditions, such as dementia, depression or psychosis have higher mortality and poorer outcomes when acutely infected with SARS-CoV-2 *(20)(21)*. Anxiety and depression are common amongst people hospitalized for COVID-19; a cohort from Wuhan, China showed that 34% experienced anxiety and 28% symptoms of depression *(24)*. Within a multinational cohort of 2088 patients admitted to ICUs, 55% had delirium which lasted a median time of 3 days *(557)*.

COVID-19 is associated with acute cerebrovascular disease (including ischaemic and haemorrhagic stroke, encephalopathy and seizures) *(556)*, and an estimated 42% increase in longer term neurological sequelae including cerebrovascular disorders, disorders of cognition, memory, movement and sensory disorders *(555)*.

Clinical characterization in children: Children have similar clinical manifestations of COVID-19 to adults, although typically with milder and less frequent symptoms, and significantly lower rates of severe disease and death *(35)(36)(37)(38)*. The clinical findings overlap with those of multiple other clinical syndromes (e.g. pneumonia, bronchiolitis, gastroenteritis and common febrile illnesses) with fever or chills and cough being the most common reported symptoms *(39)(40)*. Infants may have difficulty feeding and fever without an obvious source *(39)(41)*.

As in adults, children with underlying medical conditions are at risk for severe disease, and chronic pulmonary disease (including asthma), obesity, neurological and developmental conditions, cardiovascular disease and immunosuppression conditions are the most frequently reported risk factors *(42)*. Severe disease in children is associated with: elevated inflammatory markers (e.g. CRP, procalcitonin, interleukin 6, ferritin, D-dimer) at admission or during hospitalization; dyspnoea, tachypnoea, and/or hypoxia at admission; and gastrointestinal symptoms *(43)(44)*.

A rare multi-system inflammatory syndrome in children and adolescents (MIS-C) can cause a pattern of multi-organ failure and shock resembling Kawasaki disease *(47)*. Estimated rates from the United States are 55/100 000 children during Alpha wave, falling to 3.8/100 000 during Omicron *(554)*. Features include persistent fever, hypotension, gastrointestinal symptoms, rash, myocarditis, and laboratory evidence of increased inflammation often without respiratory symptoms *(48)(49)*.

Clinical characterization in pregnant women: Pregnant and recently pregnant people with COVID-19 are less likely to be symptomatic (OR=0.66, 95% CI 0.52–0.86; systematic review of 15 studies including 2 017 808 women), and less frequently manifest common symptoms such as fever, dyspnoea, cough and myalgia, compared with non-pregnant women of reproductive age *(50)*. These 2022 data draw from studies of pregnant people managed in hospitals for any reason, with limited data on women

during early pregnancy or postpartum. However, compared with non-pregnant women of reproductive age with COVID-19, pregnant people have higher odds of ICU admission (OR=2.61, 95% CI 1.84–3.71; 10 studies, 2 027 360 women), and invasive ventilation (OR=2.41, 95% CI 2.13–2.71; 8 studies, 1 889 174 women). Poor outcomes – severe COVID-19, admission to ICU, invasive ventilation and maternal death – are associated with older maternal age, high BMI, non-white ethnicity, any pre-existing comorbidities including chronic hypertension and diabetes, and pregnancy-specific complications such as gestational diabetes and pre-eclampsia.

Post COVID-19 condition: Most patients with COVID-19 infection recover fully, but some develop post COVID-19 condition (PCC) with medium to long-term effects on one or more body systems. Approximately 400 million people have been affected since the beginning of the pandemic *(572)*.

To recognize the condition and its impact on people's lives, WHO developed a clinical case definition of post COVID-19 condition by Delphi methodology *(573)*:

Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS- CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others which generally have an impact on everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.

A separate clinical case definition for children and adolescents has been produced, through a process of expert consensus, to fill in equity gaps for young people in obtaining a diagnosis and potentially access to services *(574)*.

Global estimates indicate that 6.2% of individuals (95% CI 2.4% - 13.3%) with symptomatic COVID-19 infection develop post COVID-19 condition. Of these, approximately 15% of patients may continue to have symptoms at 12 months *(575)*. These data come from people who suffered COVID-19 early in the pandemic, and there is a very large variation in estimates. More recent research shows the chances of developing post COVID-19 condition following COVID are reducing, but these data are limited and mostly from high-income countries *(576)*. Continued circulation of SARS-CoV2 globally means that post COVID-19 condition remains a substantial and ongoing challenge to global public health.

Some people are more likely to develop post COVID-19 condition including females, older adults, smokers, those who are overweight or obese or have pre-existing chronic health problems, and those whose COVID-19 was severe enough to need hospital or ICU admission *(577)*. The exact details of how post-COVID-19 condition is caused are still not completely known. There is evidence of a number of abnormalities including persistence of SARS-CoV2 virus in the body, altered immune responses and autoimmunity, and formation of microscopic blood clots (microthrombosis) among others *(578)*. Reinfections increase the risk. Therefore risk reduction with preventive measures and vaccination continues to be important *(572)*. Receiving two doses of vaccination appears to reduce the chance of developing post COVID-19 condition *(579)*.

The WHO is developing clinical practice guidelines for management of people with post COVID-19 condition. The therapeutic landscape for PCC is still very limited, but there is a considerable global effort in trials of novel approaches. People experiencing persistent limitations in function, or a protracted course of symptoms will require person-centered, comprehensive and multidisciplinary rehabilitation services delivered in collaboration with primary care practitioners and several medical specialties.

Variants of concern and severity of disease: Multiple viral lineages have emerged over the course of the COVID-19 pandemic. SARS-CoV-2 continues to evolve, and variants are tracked and risk assessed by WHO's Technical Advisory Group on SARS-CoV-2 Virus Evolution *(562)*. These include variants of concern (VOC) which are determined to substantially impact COVID-19 epidemiology, and/or worsen clinical disease severity, and/or are associated with significantly decreased vaccine protection *(563)*.

Compared with previously dominant Alpha, Beta, Gamma and Delta lineages, the most recent Omicron lineages demonstrate a wide spectrum of mutations and sub-lineages with high immune escape and upper airway tropism *(564)*. Omicron variants have out-competed others *(4)(105)(110)*, but in systematic reviews are associated with lower risk of hospitalization, ICU admission, oxygen therapy, ventilation and death compared with Delta variants *(553)(552)*.

Rates of disease have fallen and outcomes have improved, driven in part by temporal changes in global immunity resulting from natural and vaccine exposure. However, there remains a substantial risk for severe illness; Omicron caused more than 1.2 million deaths in 2022. Despite the declining availability of statistics, thousands of deaths are reported every week through 2024 *(4)*, and vaccine effectiveness reduces over time *(551)*. Clinically vulnerable population remain at high risk, including people at the extremes of age, those with comorbidities, frailty, and people who remain unvaccinated.

These guidelines address the ongoing need to optimize clinical treatment of COVID-19 to reduce morbidity and mortality.

Guideline development and implementation

What triggered this version of the guideline?

As COVID-19 epidemiology and severity has changed, and as emergency measures have subsided, the evidence behind a number of recommendations has changed. In parallel, evolution of health systems and the global environment have meant that the recommendations are implemented in a very different context in 2024 compared with 2020. All existing recommendations within the guideline have therefore been reassessed for scope and relevance. Where recommendations are non-specific to COVID-19 but relate to severe acute respiratory infection (SARI) more broadly, these will be incorporated into planning for a generic SARI guideline.

The new recommendations on use of antibiotics were prompted by the publication of data from a systematic review and meta-analysis, and the pressing need to address antimicrobial resistance.

How to access and use this guideline?

This guideline is available from WHO, and in web-based format in MAGICapp for user-friendliness and ease of navigation *(56)*. This allows users to easily find recommendations and to drill down into supporting evidence and tools for shared decision-making.

The guideline is also available in PDF format from the WHO website.

Additional educational modules and implementation tools for health workers can be found via:

- WHO Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation;
- WHO Openwho.org clinical management course series;
- WHO Academy.

2. METHODS

Related guidelines
This living WHO guideline for the clinical management of COVID-19 is published in PDF format (*Therapeutics and COVID-19: living guideline*) *(120)*, also published in the BMJ *(58)* and available in MAGICapp.

Timing
This guideline aims to be trustworthy and living; dynamically updated and globally disseminated as new evidence warrants a change in recommendations for COVID-19, expecting at least two updates per year.

Identifying recommendations

Each recommendation in this document is identified by a coloured box (which describes the strength of a GRADE methodology-based recommendation), or a green tick, yellow exclamation, or red cross as below which indicates that the recommendation was not formulated from a full GRADE-based approach).

Icons used where GRADE methodology does not apply

	The GREEN symbol denotes a non-GRADE-based strong recommendation of a best practice statement in favour of an intervention.
	The YELLOW symbol denotes a non-GRADE-based conditional recommendation in favour of an intervention, or a recommendation where special care is required in implementation.
	The RED symbol denotes a non-GRADE-based recommendation or best practice statement against an intervention.

Current update

Step-wise approach

The approach to guideline production is described below, although for efficiency various processes occurred simultaneously.

For version 8, a review of the scope of the entire guideline was undertaken in order to identify recommendations which were no longer pertinent, no longer specific to COVID-19, or where changes in the evidence base or implementation landscape suggested a re-evaluation was appropriate (see "Guideline pruning", below).

Step 1: Evidence monitoring and mapping and triggering of evidence synthesis
Regular monitoring of evidence around key topics occurs with support from the WHO rapid review team and their network of collaborators, overseen by the WHO steering committee. The trigger for producing or updating specific recommendations is based on a likelihood to change practice and relevance to a global audience.

In this case (version 8), a new systematic review and meta-analysis became available, and therefore triggered an evaluation.

Step 2: Convening the Guideline Development Group (GDG) - see also "Acknowledgements"
WHO selected GDG members to ensure global geographical representation, gender balance, and appropriate technical and clinical expertise. The technical unit collected and managed written declarations of interests (DOIs), and verbal updates at the start of each meeting. No verbal conflicts were declared. Web searches were undertaken by the technical team to identify any additional interests that could affect an individual's objectivity and independence during the development of the recommendations.

The GDG convened on 18 June 2024, to address the use of antibiotics in COVID-19.

Step 3: Evidence synthesis
The new evidence synthesis for antibiotic use, including methods is available within this guideline *(584)*.

Step 4: Development of recommendations
The GDG panel members are responsible for the following critical activities:

- to advise on the priority questions and scope of the guideline;
- to advise on the choice of important outcomes for decision-making;
- to comment on the evidence used to inform the guideline;
- to advise on the interpretation of the evidence, with explicit consideration of overall balance of risks and benefits;
- to formulate recommendations, taking into account diverse values and preferences according to GRADE.

The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations *(123)(125)*. Good practice statements can be made in addition to, or instead of a recommendation when a large body of indirect evidence, made up of linked evidence including several indirect comparisons, strongly supports the net benefit of the recommended action, if deemed that it will be an onerous and unproductive exercise to collect the indirect linked evidence supporting the recommendations. However, it still requires transparency and explicitness, with a clear rationale for the approach. *A priori* voting procedures were established in case required.

The following key factors were used to formulate transparent and trustworthy recommendations:

- absolute benefits and harms for all patient-important outcomes through structured evidence summaries;
- quality/certainty of the evidence *(123)(127)*;
- values and preferences of patients *(59)*;
- resources and other considerations (including considerations of feasibility, applicability, equity) *(59)*;
- each outcome will have an effect estimate and confidence interval, with a measure of certainty in the evidence, as presented in summary of findings tables. If such data are not available narrative summaries will be provided;
- recommendations will be rated as either conditional or strong, as defined by GRADE. If the panel members disagree regarding the evidence assessment or strength of recommendations, WHO will apply voting according to established methods.

Step 5: External and internal review - see also “Acknowledgements”
The WHO guideline was reviewed by pre-specified internal and external reviewers, and then approved by the WHO Guideline Review Committee. The Members of the External Review Group reviewed the guideline document to identify any factual errors, and to comment on clarity of the language, contextual issues and implications for implementation. The technical unit collected and managed declarations of interests (DOIs) and found no External Review Group member to have a conflict of interest.

Benefits and harms

For these recommendations, the GDG members prioritized outcomes (rating from 9 [critical] to 1 [not important]) with severe and critical COVID-19, taking a patient perspective (Table 14.1).

Minimum important thresholds

Pre-defined thresholds for minimum important clinical differences were agreed by the GDG before formulating recommendations. These were:

- endotracheal intubation: 1.5% (15 per 1000 patients),
- hospitalization: 1.5% (15 per 1000),
- reduction in symptoms: 1 day,
- mortality: 5% (50 deaths per 1000 patients).

Values and preferences
Specific deliberations on values and preferences and associated feasibility and resource-related considerations are presented for each recommendation.

Guideline pruning

Rationale

It is not only evidence that changes over time: the environment in which evidence is applied varies depending on multiple factors including societal change, risk perception, alternative available interventions, and the frameworks in which medical care is delivered. During the initial phases of the pandemic, there was both a singular focus on SARS-CoV2 as a pathogen, and significant uncertainty about the degree to which COVID-19 should be treated differently to respiratory disease. At that time, a large number of recommendations were good practice statements which were intended to be helpful during a health emergency, and for which minimal evidence was available contemporaneously.

There is therefore a periodic need to reassess living guidelines in the face of these important changes in order to maintain their relevance, decrease the potential for confusion or misapplication, and ensure that clinical pathways are as simple and integrated as possible.

Process

The WHO COVID-19 guideline steering committee approved the process of pruning under which each recommendation was re-evaluated for relevance, and for ongoing need. To do this, a subgroup of the GDG incorporating the methodology and clinical chairs discussed each in turn.

Consensus was sought on the action required, which could be primarily: up to date [no action]; superceded by another WHO guideline [remove and link]; likely new evidence requiring GRADE evaluation [timetable for re-examination with new evidence synthesis]; inconsistent with more recent evolution in practice or regulation [remove]; good practice statement requiring attention [remove or re-evaluate with evidence]; non-specific for COVID-19, and covered in broader WHO guidance [remove].

Each decision was recorded, and a summary table is available in Annex 6.

The whole guideline, including the list and justification for pruning, was re-presented to the full GDG for approval.

Previous versions

Versions 1 and 2 of this document were developed in consultation with the International Forum for Acute Care Trialists (InFACT), the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) and the Surviving Sepsis Campaign 2019 and were adapted from the previously published *Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus (MERS-CoV) infection is suspected: interim guidance (117)*.

For **version 3** of the COVID-19 clinical guideline the WHO Steering Committee expanded the scope from the previous versions to include recommendations on the full spectrum of disease (mild, moderate in addition to severe) and the full patient care pathway, from screening to rehabilitation. A GDG comprising individuals with broad expertise spanning multiple specialties and all regions was convened. Because of the accelerated timeline and very broad scope of the third version of the guideline, it was not feasible to undertake a formal GRADE process (PICO questions; systematic reviews; formal documentation of values and preferences; and incorporation of considerations of costs, resources, and feasibility) for each recommendation. Instead, PICOs were drafted and published evidence was synthesized under the coordination of the Science Division. The WHO Steering Committee drafted the recommendations about interventions based on these reviews. These draft recommendations and evidence summaries were pre-circulated to the GDG. The GDG was convened over multiple meetings, and consensus was achieved for all recommendations. The direction and strength of recommendations were presented using symbols rather than formal GRADE terminology (strong and conditional recommendations with grading of certainty of evidence, or best practice statements).

Subsequent versions of the guideline made new recommendations, using an innovative dynamic updating process. The methods are aligned with the *WHO Handbook for guideline development (57)*.

In **version 4**, three recommendations were made to use non-invasive (HFNO and continuous positive airway pressure) devices in hospitalized patients with COVID-19 that are severe or critical with acute hypoxic respiratory failure. Two systematic reviews/meta-analyses, one based on direct PICO (COVID-19 patients), and the other based on an indirect PICO (patients with ARDS and hypoxaemic respiratory failure) provided the data for the development of these recommendations.

In **version 5**, the guideline development considered one overarching PICO for adult post COVID-19 condition population (WHO clinical case definition, ≥19 years old), disaggregated by age and gender. The GDG made 16 conditional recommendations and one strong recommendation. Following a scoping review commissioned by the WHO Rehabilitation Programme with support from the Quality Assurance of Norms and Standards (QNS) unit, recommendations were derived from the independent systematic review and indirect evidence by Cochrane systematic reviews (Annex 6, 7 and 8)

In **version 6,** three recommendations were made based on direct and indirect systematic review and meta-analysis, and a scoping review *(3)*. PICOs were: 1) isolation for 5 days; and 2) removal of isolation based on negative rapid antigen test as compared with

earlier WHO recommendations (for symptomatic patients: 10 days after symptom onset plus 3 additional days without symptoms; and for asymptomatic patients: 10 days after positive test). Moreover, subgroup analysis for asymptomatic and symptomatic patients, and the use of antigen testing for de-isolation and estimation of number for hospitalization and/or death by simple modelling was conducted.

In **version 7**, a newly available systematic review and meta-analysis was available to inform a recommendation on awake prone positioning in non-intubated patients with COVID-19. The GDG made a conditional recommendation based on moderate/low certainty evidence for prone positioning of severely ill patients hospitalized with COVID-19 requiring supplemental oxygen (includes high-flow nasal oxygen [HFNO]) or non-invasive ventilation.

3. RECOMMENDATIONS

Who do the recommendations apply to?

The recommendations in the clinical management living guidelines are broadly applicable to anyone involved, directly or indirectly, in the care of patients with COVID-19. This includes clinicians, allied health care workers and hospital administrators.

This guideline applies to all patients with COVID-19. Recommendations may differ based on the severity of COVID-19, according to WHO severity definitions (see below) *(6)*.

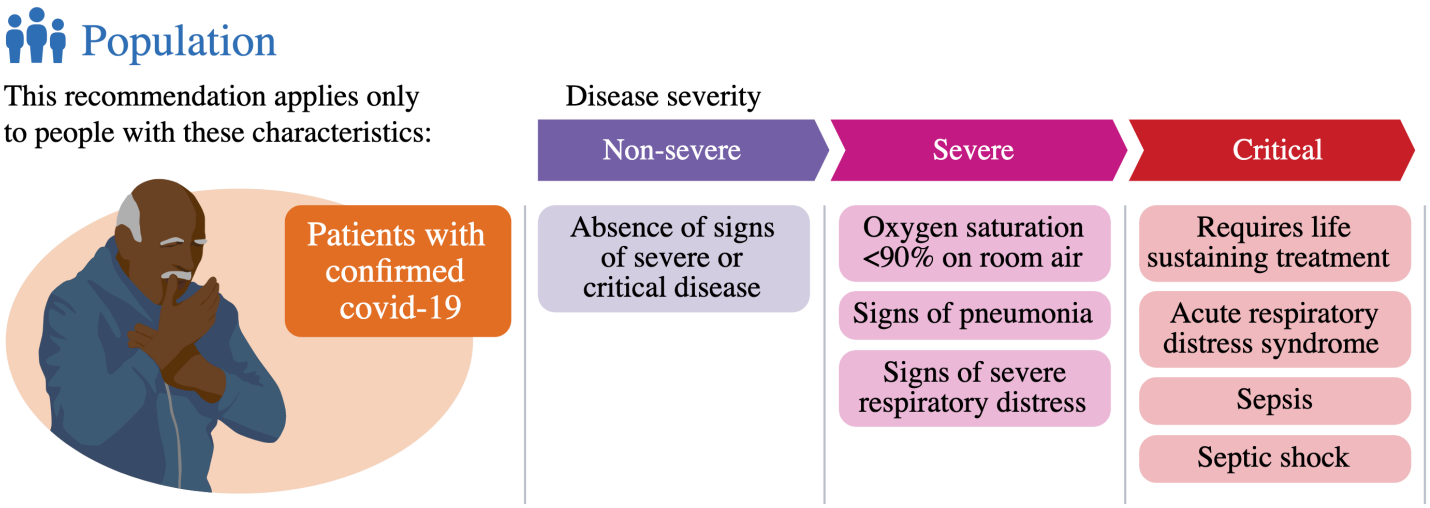
WHO definitions of disease severity for COVID-19

- **Critical COVID-19** – Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.

- **Severe COVID-19** – Defined by any of:
  - oxygen saturation < 90% on room air;
  - severe pneumonia;
  - signs of severe respiratory distress (in adults, accessory muscle use, inability to complete full sentences, respiratory rate > 30 breaths per minute; and, in children, very severe chest wall in-drawing, grunting, central cyanosis, or presence of any other general danger signs including inability to breastfeed or drink, lethargy, convulsions or reduced level of consciousness).
- **Non-severe COVID-19** – Defined as the absence of any criteria for severe or critical COVID-19.

Caution: The GDG noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary, and should be interpreted cautiously when defining disease severity. For example, clinicians must use their judgment to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, clinicians may interpret a saturation of 90–94% on room air as abnormal in the patient with normal lungs, and as an early sign of severe disease in patients with a downward clinical trajectory. Generally, in cases where there is doubt, the GDG suggested erring on the side of considering disease as severe.

The infographic illustrates these three disease severity groups and key characteristics to apply in practice.



Infographic co-produced by the BMJ and MAGIC; designer Will Stahl-Timmins (see BMJ Rapid Recommendations).

3.1 COVID-19 care pathway

For the most up to date clinical practice guideline on therapeutics and COVID-19 see WHO website and BMJ website and MAGICapp.

3.1.1 Immediate implementation of appropriate infection prevention and control measures

For information on Infection Prevention and Control for COVID-19, please see the following links:

1. *Infection prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed (137)*.
2. *Infection prevention and control in the context of coronavirus disease (COVID-19): A living guideline* (in MAGICapp).

3.1.2 Screening, triage and early recognition of patients with COVID-19

The primary objective of the COVID-19 global response is to slow and stop transmission, find, isolate and test every suspect case, and provide timely appropriate care of patients with COVID-19. The recommended location of care will depend on the epidemiologic scenario and be either at a designated COVID-19 health facility, community facility or, where not possible, at home. Refer to the WHO *Operational considerations for case management of COVID-19 in health facility and community (1).*

We recommend screening all persons at the first point of contact with the health system in order to identify individuals that have suspected or confirmed COVID-19 *[Non-GRADE based recommendation]*

Remarks:

1. Screening can be performed in areas such as the emergency unit, outpatient department/primary care clinic, in the community by a community health worker or by telemedicine. In the context of this outbreak, this should be done at a distance (> 1 m). Use a simple set of questions based on the WHO case definition (see Table 6.1). This is best done by establishing screening protocols at all health access points and during contact tracing activities. Older people and those immunosuppressed may present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, delirium and absence of fever (61)(142)(144). Thus, screening questions may need to be adjusted for certain settings and guided by epidemiologic considerations.
2. Persons with symptoms (see Table 6.1) that meet the case definition for suspected COVID-19 enter into the COVID-19 care pathway and should immediately be given a medical mask and directed to a single room. If a single room is not possible, then group patients with similar clinical diagnosis and based on epidemiological risk factors, with a spatial separation (at least 1 m between patients). Suspected cases should not be cohorted together with confirmed cases.
3. In areas with other endemic infections that cause fever, such as malaria, dengue, tuberculosis (TB) etc., as part of screening, febrile patients should be tested as per routine protocols (146)(148)(62)(151)(153)(154)(582), irrespective of the presence of respiratory signs and symptoms. Coinfection with COVID-19 may coexist.
4. When influenza virus is known or suspected to be circulating, ensure that is also considered as part of screening of patients with fever and influenza-like-illness; and that testing is per local routine protocols. Coinfection with COVID-19 may exist.
5. Large outbreaks have been observed in long-term care facilities (LTCFs) (142). The COVID-19 care pathway should be activated for all residents of LTCFs who are contacts of a confirmed case in that LTCF, including immediate isolation, testing and treatment as needed. The priority focus in these settings should be to ensure the well-being of residents and protect health workers, and implementation of clinical management and IPC that considers the individual's condition and prognosis (such as screening visitors for COVID-19) (63).

Info Box

Table 6.3 COVID-19 disease severity classification

Mild disease		Symptomatic patients (Table 6.1) meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia. See the WHO website for most up-to-date case definitions [2].
Moderate disease	**Pneumonia**	**Adolescent or adult** with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO_2 ≥ 90% on room air. **Child** with cough or difficulty breathing + fast breathing and/or chest indrawing and no signs of severe pneumonia. Fast breathing: < 2 months: ≥ 60 breaths/min; 2–11 months: ≥ 50; 1–5 years: ≥ 40. The diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications. **Caution:** The oxygen saturation threshold of 90% to define severe COVID-19 is arbitrary and should be interpreted cautiously. For example, clinicians must use their judgment to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, a saturation between 90–94% on room air may be abnormal (in patient with normal lungs) and can be an early sign of severe disease, mainly if patient is on a downward trend. Generally, if there is any doubt, the panel suggested erring on the side of considering the illness as severe..
Severe disease	**Severe pneumonia**	**Adolescent or adult** with clinical signs of pneumonia (fever, cough, dyspnoea) plus one of the following: respiratory rate > 30 breaths/min, severe respiratory distress, or SpO_2 < 90% on room air. **Child:** with clinical signs of pneumonia (cough or difficulty breathing + fast breathing or chest wall indrawing) + at least one of the following: • SpO_2 < 90% • Very severe chest indrawing, grunting, central cyanosis, or presence of any other general danger sign (inability to breastfeed or drink, lethargy or unconsciousness or convulsions). The diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Critical disease	**Acute respiratory distress syndrome (ARDS)** [107][108][109]	**Onset:** within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms. **Chest imaging:** radiograph,CT scan or lung ultrasound: bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. **Origin of pulmonary infiltrates:** respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factors present. Oxygenation impairment in adults: **Air blood gases (ABG) available** • Mild ARDS: 200 mmHg < PaO2/FiO2

		≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH_2O) • Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH_2O) • Severe ARDS: PaO2/FiO2 ≤ 100 mmHg (with PEEP ≥ 5 cmH_2O). **ABG not available (Kigali modification)** • SpO2/FiO2 < 315 suggests ARDS (including non-ventilated patients) Oxygen impairment in children: note OI and OSI.[a] Use OI when available. If PaO_2 not available, wean FiO_2 to maintain SpO2 ≤ 97% to calculate OSI or SpO2/FiO2 ratio: • Bilevel (NIV or CPAP) ≥ 5 cmH2O via full face mask: PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤ 264 • Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5 • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 • Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥12.3. [a] Oxygenation Index (OI) is an invasive measurement of the severity of hypoxaemic respiratory failure and may be used to predict outcomes in paediatric patients. It is calculated as follows: percentage of fraction of inhaled oxygen multiplied by the mean airway pressure (in mmHg), divided by the partial pressure of arterial oxygen (in mmHg), divided by the partial pressure of arterial oxygen (in mmHg). Oxygen Saturation Index (OSI) is a non-invasive measurement and has been shown to be a reliable surrogate marker of OI in children and adults with respiratory failure. OSI replaces PaO_2 with oxygen saturation as measured by pulse oximetry (SpO_2) in the OI equation.
	Sepsis [110][111]	**Adults:** acute life-threatening organ dysfunction caused by a dysregulated host response to suspect or proven infection. Signs of organ dysfunction include: altered mental status (delirium), difficult or fast breathing, low oxygen saturation, reduced urinary output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinaemia. **Children:** suspected or proven infection and ≥ 2 age-based systemic inflammatory response syndrome (SIRS) criteria,[b] of which one must be abnormal temperature or white blood cell count. [b] SIRS criteria: abnormal temperature (> 38.5 °C or < 36 °C); tachycardia for age or bradycardia for age if < 1 year; tachypnoea for age or need for mechanical ventilation; abnormal white blood cell count for age or > 10% bands.
	Septic shock [110][111]	**Adults:** persistent hypotension despite volume resuscitation, requiring vasopressor to maintain MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L. **Children:** any hypotension (SBP < 5th centile or 2SD below normal for age) or two or three of the following: altered mental status; bradycardia or tachycardia (HR < 90 beats/min [bpm] or < 160 bpm in infants and heart rate < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or weak pulse; fast breathing; mottled or cool skin or petechial or purpuric rash; high lactate; reduced urine output; hyperthermia or hypothermia.
	Acute thrombosis	Acute venous thromboembolism (i.e. pulmonary embolism), acute coronary syndrome, acute stroke.

	MIS-C	Preliminary case definition: children and adolescents 0–19 years of age with fever ≥ 3 days AND two of the following: rash or bilateral non purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet); hypotension or shock; features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP); evidence of coagulopathy (PT, PTT, elevated D-dimers); acute gastrointestinal problems (diarrhoea, vomiting or abdominal pain); AND elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin AND no other obvious microbial cause of shock syndrome AND evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19. (See scientific brief, 15 May 2020, WHO: *Multisystemic inflammatory syndrome in children and adolescents temporally related to COVID-19*.)

Note: If altitude is higher than 1000 m, then the correction factor should be calculated as follows: PaO_2/FiO_2 x barometric pressure/760.

Abbreviations: BP blood pressure; bpm beats per minute; CPAP continuous positive airway pressure; CT computed tomography; FiO_2 fraction of inspired oxygen; MAP mean arterial pressure; NIV non-invasive ventilation; OI Oxygenation Index; OSI Oxygenation Index using SpO_2; PaO_2 partial pressure arterial oxygen; PEEP positive end-expiratory pressure; SBP systolic blood pressure; SD standard deviation; SIRS systemic inflammatory response syndrome; SOFA sequential organ failure assessment; SpO_2 oxygen saturation.

3.1.2.1 Assessment and recognition

All areas where severe patients may be cared for should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (nasal cannula, Venturi mask and mask with reservoir bag) *[Non-GRADE-based recommendation].*

Remark:
This includes areas in any part of health facilities, including emergency units, critical care units, primary care/outpatient clinics, as well as pre-hospital settings and ad hoc community facilities that may receive patients with severe COVID-19. See WHO Oxygen sources and distribution for COVID-19 treatment centres (132).

3.1.3 Laboratory diagnosis

This guidance brings together diagnostic technical guidance developed and published since the beginning of the COVID-19 pandemic.

1. *Antigen-detection in the diagnosis of SARS-CoV-2 infection (184)*;
2. *Use of SARS-CoV-2 antigen-detection rapid diagnostic tests for COVID-19 self-testing (186)*; and
3. *Diagnostic testing for SARS-CoV-2 interim guidance* regarding specimen collection, processing and laboratory testing and the diagnostic algorithm *(188)*.

Nucleic acid amplification testing (NAAT) and antigen testing

We recommend, for all suspect COVID-19 cases, at minimum the collection of respiratory specimens for nucleic acid amplification testing (NAAT) for example reverse transcription polymerase chain reaction (RT-PCR). Repetitive testing of upper respiratory tract (URT) and/or lower respiratory tract (LRT) might be needed to establish a diagnosis *(190)***. Additional samples that might aid the diagnosis of COVID-19 can be faecal specimens (if appropriately validated by the receiving laboratory). If deceased consider the collection of postmortem specimens** *(188)***. In addition, testing for other respiratory viruses and bacteria should be considered when clinically indicated according to local guidelines.** *[Non-GRADE-based recommendation].*

Remarks:

1. Use appropriate PPE for specimen collection (droplet and contact precautions for URT specimens; airborne precautions for LRT specimens). See IPC guidelines (also refer to chapter 5 on IPC) for the most up-to-date guidance (192)(194).
2. In the first week of symptom onset relatively high viral loads are generally observed in the upper respiratory tract (URT) specimens. For the collection of URT samples, we recommend the collection of nasopharyngeal and oropharyngeal specimens. When collecting URT samples, use viral swabs (sterile Dacron or rayon, not cotton), for nasopharyngeal swabbing use a swab with a long flexible shaft designed for nasopharyngeal sampling. For instructions on appropriate URT sampling see Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation (161). Unless specified differently by the receiving laboratory, transport sample in viral transport media.
3. LRT (vs URT) samples are more likely to be positive after the first week of illness. Thus if URT are negative and clinical suspicion remains, also collect specimens from the LRT when readily available (expectorated sputum, or endotracheal aspirate/ bronchoalveolar lavage in ventilated patient). Clinicians may elect to collect only LRT samples when these are readily available (for example, in mechanically ventilated patients). Sputum induction should be avoided owing to increased risk of aerosol transmission. In a patient with suspected COVID-19, especially with pneumonia or severe illness, a single negative URT sample does not exclude the diagnosis, and additional URT and LRT samples are recommended (188). In hospitalized patients with confirmed COVID-19, repeated URT and LRT samples can be collected, as clinically indicated, but are no longer indicated for release from COVID-19 precautions (60).
4. NAAT testing is the reference method for the diagnosis of COVID-19. However, antigen testing can be used to diagnose current COVID-19 infection, especially in situations, where NAAT is unavailable or where prolonged turnaround times preclude clinical utility. . For details on appropriate utilization of antigen testing see interim guidance Antigen-detection in the diagnosis of SARS-CoV-2 infection (196). If antigen testing is used, assure that sample collection and testing is performed according to the instructions for use of the antigen tests, staff are appropriately trained and testing quality is embedded within an overall national testing programme. Ag-RDTs can also be used by individuals to test themselves, termed COVID-19 self testing. When used by someone who is a suspected case of COVID-19, a positive self-test result is consistent with current COVID-19 but a negative self-test result does not rule out infection. For more details. see interim guidance Use of SARS-CoV-2 antigen-detection rapid diagnostic tests for COVID-19 self-testing (186).

Antibody (serological) testing

SARS-CoV-2 antibody tests are not recommended for diagnosis of current infection with COVID-19 *[Non-GRADE-based recommendation]***.**

Remarks:

1. If repetitive negative NAAT/RT-PCR results are obtained from a patient in whom COVID-19 is strongly suspected, a paired serum specimen could be collected. One specimen taken in the acute phase and one in the convalescent phase 2–4 weeks later. This is only useful if validated (semi) quantitative serology assays and trained staff for the interpretations are available in the receiving laboratory. With these paired samples it can be retrospectively evaluated whether there is seroconversion or a rise in antibody titres, further supporting the suspicion that this individual indeed had recent COVID-19 despite negative NAAT results.

3.1.4 COVID-19 Self-testing

Strong recommendation for

COVID-19 self-testing, using SARS-CoV-2 Ag-RDTs, should be offered in addition to professionally administered testing services *[Strong recommendatoin, low to moderate certainty evidence]*

For full recommendations and additional details, see: *Use of SARS-CoV-2 antigen-detection rapid diagnostic tests for COVID-19 self-testing (186).*

Remarks:

Human rights: COVID-19 self-testing is a personal choice. It can expand access to testing by providing an additional way for people to test and make personal risk-based decisions that may affect their health and the health of their families and communities (e.g. to protect those most affected by or who may be at increased risk of severe COVID-19, or to enable individual participation in activities). COVID-19 self-testing, as with any testing, should always be voluntary and never mandatory or coercive. The practice of self-testing, regardless of test results, must always be free from stigma and discrimination. Self-testers will need to be provided with adequate information on when to test and nationally relevant post-test responsibilities and actions. Anyone uncertain of their COVID-19 self-testing result, or desiring alternative professional testing services, should be encouraged to access other testing options where available and in line with the latest national guidance. Countries should consider reviewing and contextualizing their existing policies on the age of consent to include COVID-19 self-testing and the role of assisted and caregiver-led self-testing by a parent or guardian. For adolescents and mature minors, age-of-consent policies that enable access without parental consent are important to enable COVID-19 self-testing when needed.

Epidemiology: The implications of a test result are not only a function of its inherent sensitivity and specificity. The result is also dependent on the prevalence of SARS-CoV-2 infection in the population prioritized for testing. When using COVID-19 self-testing in settings with higher pre-test probability, i.e. higher likelihood of an individual having SARS-CoV-2 infection, such as in places where there is ongoing community transmission or when an individual is at high likelihood of exposure (e.g. contacts, health and care workers), the positive predictive value of the test is high. This means a positive self-testing result is likely to be a true positive. When COVID-19 self-testing is used in a low pre-test probability setting (e.g. when testing someone without symptoms and no known exposure to the virus or when there is no or low community transmission), the positive predictive value of self-testing is lower, which will lead to increased false-positive results. In these situations, the negative predictive value of COVID-19 self-testing is high, meaning the risk of a false negative is lower.

Evolving context, priorities and messaging: Health worker and community awareness of and engagement in adapting COVID-19 self-testing is important for successful implementation. As local epidemiology changes, information on self-testing that is context-specific, correct, clear, concise and age-appropriate should be made available. Messaging should include when self-testing should be prioritized or deprioritized for specific populations or settings, the meaning of a positive or negative self-test result and any recommended follow-up actions after self testing. Messages will vary based on current local situations but should be consistent with national policies.

Emerging SARS-CoV-2 variants: This recommendation is valid for detection of all reported SARS-CoV-2 variants of concern. As SARS-CoV-2 continues to evolve, policies will need to take into consideration circulating variants and test performance. The accuracy of COVID-19 self-testing needs to be continually assessed and reviewed with the emergence and spread of new variants, just as it is for professional-use NAAT and Ag-RDT.

3.1.5 Infectious period and isolation

Conditional recommendation for

We suggest 10 days of isolation for individuals who are symptomatic due to SARS-CoV-2 infection *[Conditional recommendation, very low certainty evidence].*

We suggest 5 days of isolation for individuals who are asymptomatic with SARS-CoV-2 infection *[Conditional recommendation, very low certainty evidence].*

Evidence to decision

Benefits and harms

The benefits outlined by the GDG relate to the impact on subsequent hospitalization and mortality across contacts (very low certainty evidence) of a 10-day, compared with a 5-day, isolation period for symptomatic individuals. **Symptomatic individuals are much more likely to test positive than asymptomatic individuals and thus much more likely to transmit SARS-CoV-2**. This provides the rationale, despite the very low certainty evidence on the impact of isolation on subsequent transmission, hospitalization, and mortality, for the suggestion for 10 days in symptomatic and 5 days in asymptomatic cases. A shortened isolation period, where safe, was agreed-upon as preferable as part of the values and preferences, which further informed the recommendation for 5 days of isolation for asymptomatic individuals.

Harms of varying periods of isolation, such as mental health, financial or social impacts, were not formally incorporated into the evidence review, given the uncertainty involved.

Certainty of the evidence

The evidence reviewed to inform this recommendation was deemed to be of very low certainty, rated down due to the high degree of uncertainty in the parameters that inform the model and the indirectness of the data. Specifically, there is a great deal of uncertainty across the following assumptions: i) the infectivity of individuals with positive rapid antigen test; ii) the effective reproduction number; iii) the assumed hospitalization rate of infected individuals; and iv) the assumed case-fatality rate of infected individuals. Additional sources of uncertainty lie in understanding the contributing role of different public health measures in place in different regions of the world, vaccination status, history of prior infection and the infecting SARS-CoV-2 VoC and resultant changes to infectivity and severity. Evidence was reviewed regarding the duration of viral culture positivity and PCR positivity, which were both deemed to be of very low certainty.

A large source of uncertainty, as voiced by the GDG and not consistently defined in the available evidence, was the definition of what constituted symptomatic infection. From clinical experience, noted by the GDG, classifying patients as either symptomatic or asymptomatic was not always straightforward.

Values and preferences

- Given anticipated strong preferences in most individuals for shorter periods of isolation, and the positive social and economic consequences of shorter periods of isolation, the GDG placed a high value on shorter periods of isolation.
- Despite the very low certainty evidence, the GDG placed a high value on the possible increase, in symptomatic patients, of transmission and resulting hospitalization from a shorter period of isolation.
- The GDG nevertheless acknowledged the substantial variability in these values and preferences that are likely to exist.

Resources and other considerations

The GDG emphasized that there are substantial resource considerations in asking individuals with mildly symptomatic disease to isolate for 5 days. These resource considerations should be incorporated into policies to ensure that the impact of periods of isolation on individuals is minimized as it relates to financial, social, or mental health specific impacts.

Justification

The GDG emphasized that the available evidence for review was inadequate to issue a substantial change in recommendation from existing WHO guidance on duration of isolation for symptomatic individuals. The GDG emphasized that, from reviewing the evidence, there were likely important differences between symptomatic and asymptomatic individuals in the likelihood of transmitting infectious virus between 5 and 10 days of isolation. The marked apparent substantially greater likelihood of transmission between days 5 to 10 in symptomatic versus asymptomatic patients led to separate recommendations for these two populations. There remains a high degree of uncertainty in accurately classifying patients into symptomatic and asymptomatic groups, but not so great as to render the differentiation inappropriate for decision-making.

The role of rapid antigen tests in determining infectivity, and inter-individual variation in duration of positivity, was highlighted as a major challenge in justifying a major change to the recommendations. This was highlighted as another major evidence gap.

The GDG discussed that hospitalization and mortality among contacts remain the crucial outcomes for consideration. Other important outcomes were not formally incorporated into the evidence evaluation, such as post-COVID-19 condition or COVID-19

disease among contacts, given the available evidence. Future iterations of this guidance may incorporate alternate outcomes such as those.

Clinical question/ PICO

Population: Asymptomatic COVID-19 patients
Intervention: Isolation for 5 days after positive test
Comparator: Isolation for 10 days after positive test

Outcome Timeframe	**Study results and measurements**	**Comparator** Isolation for 10 days	**Intervention** Isolation for 5 days	**Certainty of the evidence** (Quality of evidence)	**Summary**
Onward transmission leading to hospitalization (28 days) [1]		**9** per 1000 Difference:	**11** per 1000 **2 more per 1000** (CI 95% 2 more — 3 more)	**Very low** Due to certainty of parameters in the model and indirectness.	Whether isolation for 5 days would increase onward transmission leading to hospitalization of secondary cases is very uncertain compared with isolation for 10 days.
Onward transmission leading to death (90 days) [2]		**2** per 1000 Difference:	**3** per 1000 **1 more per 1000** (CI 95% 0 more — 1 more)	**Very low** Due to certainty of parameters in the model and indirectness.	Whether isolation for 5 days would increase onward transmission leading to mortality of secondary cases is very uncertain compared with isolation for 10 days.

1. Rapid antigen test positivity: day 5: 27% (2 studies; n=71) versus day 10: 21% (3 studies; n=368); Effective reproduction number: 0.96 (range 0.72-1.2); hospitalization rate: 4.3%
2. Rapid antigen test positivity: day 5: 27% (2 studies; n=71) versus day 10: 21% (3 studies; n=368); Effective reproduction number: 0.96 (range 0.72-1.2); case fatality: 1.05%

Clinical question/ PICO

Population: Symptomatic COVID-19 patients
Intervention: Isolation for 5 days after symptom onset
Comparator: Isolation for 10 days after symptom onset plus 3 additional days without symptoms

Outcome Timeframe	**Study results and measurements**	**Comparator** Isolation for 10 days	**Intervention** Isolation for 5 days	**Certainty of the evidence** (Quality of evidence)	**Summary**
Onward transmission leading to hospitalization (28 days) [1]		**9** per 1000 Difference:	**28** per 1000 **19 more per 1000** (CI 95% 14 more — 24 more)	**Very low** Due to certainty of parameters in the model and indirectness.	Whether Isolation for 5 days would increase onward transmission leading to hospitalization of secondary cases is very uncertain compared with isolation for 10 days.
Onward		**2**	**7**	**Very low**	Whether Isolation for 5

Outcome Timeframe	Study results and measurements	Comparator Isolation for 10 days	Intervention Isolation for 5 days	Certainty of the evidence (Quality of evidence)	Summary
transmission leading to death (90 days) [2]		per 1000 Difference:	per 1000 **5 more per 1000** (CI 95% 4 more — 6 more)	Due to certainty of parameters in the model and indirectness.	days would increase onward transmission leading to death of secondary cases is very uncertain compared with isolation for 10 days.

1. Rapid antigen test positivity: day 5: 68% (2 studies; n=211) versus day 10: 21% (3 studies; n=368); Effective reproduction number: 0.96 (range 0.72-1.2); hospitalization rate: 4.3%
2. Rapid antigen test positivity: day 5: 68% (2 studies; n=211) versus day 10: 21% (3 studies; n=368); Effective reproduction number: 0.96 (range 0.72-1.2); case fatality: 1.05%

3.1.6 De-isolation

Conditional recommendation for

We suggest the use of rapid antigen testing to reduce the period of isolation *[Conditional recommendation, very low certainty evidence]*.

Evidence to decision

Benefits and harms

The possible benefit is on average a reduction of 3 days' isolation period by using rapid tests to determine the period of isolation (very low certainty evidence).

There are minimal harms of employing rapid tests to determine the period of isolation.

Certainty of the evidence

The evidence was of very low certainty, rated down for indirectness and uncertainty in the included model parameters. Additional sources of uncertainty from the above recommendations that were not formally evaluated included evaluations of the sensitivity and specificity of various types of rapid tests, the swab technique employed, vaccination status, history of prior infection or the infecting variant, leading to greater uncertainty as assessed by the GDG.

Values and preferences

Given anticipated strong preferences in most individuals for shorter periods of isolation, and the positive social and economic consequences for shorter periods of isolation, the GDG placed a high value on shorter periods of isolation.

The GDG nevertheless acknowledges the substantial variability in these values and preferences that are likely to exist.

Resources and other considerations

The GDG acknowledged that the resource implications of prolonged periods of isolation may be considerable and reach beyond the individual, with varying social, economic, and mental health impacts. Implementation of the above recommendations should incorporate policies to ensure those considerations are addressed.

Justification

There is very low certainty evidence that using rapid antigen tests to decrease duration of isolation will have trivial effects on transmission and subsequent hospitalization.

With values and preferences of the GDG preferring shorter periods of isolation, given the uncertainty of the data, incorporating rapid antigen tests into algorithms for discontinuing isolation periods was deemed reasonable, acknowledging very low certainty of the available evidence regarding the impact of shorter periods of isolation on transmission and resulting hospitalization. There was no apparent difference across symptomatic or asymptomatic individuals in the use of rapid antigen tests to shorten the period of isolation.

Research needs

Uncertainties, emerging evidence, and future research

Despite the guidance for discontinuation of transmission-based precautions (including isolation) and release from the COVID-19 care pathway, there remain uncertain outcomes associated with the onward transmission of SARS-CoV-2 infection, as well as implications for the duration of isolation required for patients. Future research could be influenced by these uncertainties, i.e. the generation of more credible and relevant evidence for policy and practice in relation to onward transmission and adverse outcomes.

- Role and effectiveness of antigen test to accurately predict SARS CoV-2 onward transmission in symptomatic and asymptomatic patients;
- Evaluation of the sensitivity and specificity of various types of rapid tests on the onward transmission of SARS CoV-2;
- Determination of outcomes, hospitalization, ICU admission, mortality, and post COVID-19 condition and the moderation role of symptomatic and asymptomatic, variants, vaccination, and reinfections;
- Determination of optimal duration of isolation.

3.2 Management of moderate COVID-19

Patients with moderate disease may present to an emergency unit or primary care/outpatient department, or be encountered during community outreach activities, such as home visits or by telemedicine. See Table 6.3 for definition of non-severe pneumonia.

3.2.1 Use of pulse oximetry for home monitoring

Conditional recommendation for

For symptomatic patients with COVID-19 and risk factors for progression to severe disease who are not hospitalized, we suggest the use of pulse oximetry monitoring at home as part of a package of care, including patient and provider education and appropriate follow-up *[Conditional recommendation, very low certainty evidence]*.

Practical info

The GDG made a conditional recommendation for the use of home pulse oximetry monitoring. This recommendation is predicated on the availability and accessibility of high-quality and reliable pulse oximeters for home use; the integration of home pulse oximetry into a health system, from a training and human resources perspective; and targeting the intervention to patients who would likely get the most benefit, namely those at high-risk and those who are symptomatic. Also, no recommendation was made on the frequency or duration of pulse oximetry monitoring. *Note:* training on appropriate IPC (cleaning and disinfection) should be included.

Uncertainties

The panel encourage further research to clarify uncertainties, especially in low-resource settings. Research gaps remain as to ensuring standards of quality across pulse oximeter devices.

Evidence to decision

Benefits and harms	Uncertain benefits or harms

Possible theoretical benefits of home oximetry monitoring include earlier detection of and intervention for severe disease (such as more intense monitoring for deterioration or starting corticosteroid therapy), patient reassurance in case of normal values, limiting hospital strain due to prevented admission of patients who may not need acute care, and increased opportunities for patient-provider educational conversations (very low certainty).

Possible harms of home oximetry monitoring include the possibility of increased patient anxiety and stress, the possibility of increased hospital visits for patients who would otherwise not seek out hospital care, and the possibility of false reassurance with misinterpretation of the data. Low quality or inaccurate pulse oximeters, particularly with pulse oximeters not validated in different skin colours, may provide false reassurance or false alarms (very low certainty).

The GDG suggested that the possible benefits would outweigh the possible harms, and this may be most likely in specific subgroups of patients, i.e. those with symptoms and those with risk factors for severe disease. The GDG also suggested that the intervention would only have benefit in symptomatic patients with COVID-19, and that asymptomatic patients would have no benefit.

Certainty of the evidence

Very low

For key outcomes of hospitalization, mortality, mechanical ventilation, and ICU admission the panel considered the evidence to be of very low certainty.

Values and preferences

No substantial variability expected

Applying the agreed values and preferences, the GDG inferred that well-informed patients would consider the minimal possible harms associated with home oximetry monitoring to not outweigh the possible, theoretical benefits on the outcomes of hospitalization and patient satisfaction. Patient members of the panel agreed with this standard.

Resources and other considerations

Important considerations

Home oximetry monitoring is not accessible to many patients, due to lack of available equipment, lack of relevant personnel to monitor it, lack of ability to interpret the results at home, or lack of knowledge about implementation. Home pulse oximetry may be useful in certain settings, including low resource settings, particularly when hospitals are strained and where it may be necessary to effectively monitor patients in a home-based setting. However home oximetry monitoring will only be of value if the users are adequately informed on how to interpret the readings and have ready access to providers who can advise on the response to readings. Considerations for education and training of patients and providers, as well as adequate staffing, to implement care pathways with available access to acute care will need to be integrated.

Justification

When moving from evidence to the conditional recommendation for the use of home pulse oximetry monitoring for patients with COVID-19, the panel emphasized the lack of evidence in either direction and the need for high-quality clinical trials examining both patient symptoms of stress, as well as other clinical outcomes listed above. The panel also emphasized contextual factors, such as resource-considerations, accessibility, feasibility, and impact on health equity as important considerations. Ultimately, the panel thought that the theoretical benefit targeted to symptomatic and high-risk populations was notable only as part of a larger package of care including education and follow-up. Important caveats raised by the panel included the importance of integrating any intervention with education between providers and patients about the meaning of relevant output from the pulse oximeter and ability to act on results.

Subgroup analyses

There were insufficient data based on the presented data to perform any subgroup analyses.

Applicability

Special populations

There is no evidence for home pulse oximetry monitoring for patients with COVID-19 in special populations. Considerations for implementation and applicability centred around focusing on higher-risk populations, where benefits would be most notable. Please see Table 7.2 for information on definitions of who would be considered high-risk for this implementation.

Clinical question/ PICO

Population: Patients treated at home with confirmed or suspected COVID-19 disease
Intervention: SpO2 < 92% (Pulse oximetry use at home)
Comparator: SpO2 ≥ 92% (Pulse oximetry use at home)

Outcome Timeframe	**Study results and measurements**	**Comparator** SpO2 ≥ 92% (Pulse oximetry use at home)	**Intervention** SpO2 < 92% (Pulse oximetry use at home)	**Certainty of the evidence** (Quality of evidence)	**Summary**
Hospitalization	Relative risk 7 (CI 95% 3.4 — 14.5) Based on data from 77 participants in 1 studies. (Observational (non-randomized))	**103** per 1000 Difference:	**840** per 1000 **737 more per 1000** (CI 95% 453 more — 1,597 more)	**Very low** Due to serious risk of bias, Due to serious imprecision [1]	SpO2 <92% possibly increases need for hospitalization
ICU admission	Relative risk 9.8 (CI 95% 2.2 — 44.6) Based on data from 77 participants in 1 studies. (Observational (non-randomized))			**Very low** Due to serious risk of bias, Due to serious imprecision [2]	SpO2 <92% possibly increases need for ICU admission
ARDS	Relative risk 8.2 (CI 95% 1.7 — 38.7) Based on data from 77 participants in 1 studies. (Observational (non-randomized))			**Very low** Due to serious risk of bias, Due to serious imprecision [3]	SpO2 <92% possibly increases the risk of ARDS
Septic shock	Relative risk 6.6 (CI 95% 1.3 — 32.9) Based on data from 77 participants in 1 studies. (Observational (non-randomized))			**Very low** Due to serious risk of bias, Due to serious imprecision [4]	SpO2 <92% possibly increases the risk of septic shock
Hospitalization	Based on data from participants in 2 studies. (Observational (non-randomized))	Two small single arm (no comparator group) studies that offered home monitoring to patients discharged from emergency department. 3/20 (150 per 1000) and 6/52 (115 per 1000) of patients using home SpO2 monitors required hospitalization.		**Very low** Due to serious risk of bias, Due to serious imprecision [5]	No data re whether home SpO2 monitoring vs no monitoring affects hospitalization rates

1, 2, 3, 4, 5. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**

3.3 Management of severe COVID-19

3.3.1 Use of blood cultures

For COVID-19 patients with severe or critical disease, collect blood cultures, ideally prior to initiation of antimicrobial therapy *[Non-GRADE-based recommendation].*

Remark:
If blood cultures cannot be taken timely before the administration of antimicrobial therapies, indicate the details of administered antibiotics on the laboratory request.

Justification

See recommendations on use of antibiotics in COVID.

3.3.2 Supplemental oxygen

We recommend immediate administration of supplemental oxygen therapy to any patient with emergency signs during resuscitation to target SpO_2 ≥ 94% and to any patient without emergency signs and hypoxaemia (i.e. stable hypoxaemic patient) to target SpO_2 > 90% or ≥ 92–95% in pregnant women *[Non-GRADE-based recommendation].*

Remarks for adults:
1. Adults with emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma and/or convulsions) should receive emergency airway management and oxygen therapy during resuscitation to target SpO_2 ≥ 94% (159)(128).
2. Once the patient is stable, target > 90% SpO_2 in non-pregnant adults and ≥ 92–95% in pregnant women.
3. Deliver oxygen flow rates using appropriate delivery devices (e.g. use nasal cannula for rates up to 5 L/min; Venturi mask for flow rates 6–10 L/min; and face mask with reservoir bag for flow rates 10–15 L/min). For more details about oxygen titration, refer to the WHO Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation (161).
4. In adults, techniques such as positioning, e.g. high supported sitting, may help to optimize oxygenation, ease breathlessness and reduce energy expenditure (221).
5. In adult patients with evidence of increased secretion production, secretion retention, and/or weak cough, airway clearance management may assist with secretion clearance. Techniques include gravity-assisted drainage and active cycle of breathing technique. Devices including mechanical insufflation-exsufflation and inspiratory positive pressure breathing should be avoided where possible. Implementation of techniques should be tailored to the individual patient and follow available guidelines (221).
Remarks for children:
1. Children with emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma or convulsions) should receive emergency airway management and oxygen therapy during resuscitation to target SpO_2 ≥ 94% (159)(128)(130).
2. Once patient is stable, the target is > 90% SpO_2 (130).
3. Use of nasal prongs or nasal cannula is preferred in young children, as they may be better tolerated.

3.3.3 Awake prone positioning (updated 18 August 2023)

Prone positioning is an intervention aimed at ameliorating poor oxygenation in patients with acute hypoxaemic respiratory failure. It has been mostly used in patients receiving mechanical ventilation *(542)(543)*. During the pandemic, interest in awake prone positioning peaked as a result of the previously demonstrated benefit in mechanically ventilated patients. The physiological objective of prone positioning is to improve lung mechanics and gas exchange, with improved downstream clinical outcomes.

Awake prone position may be a treatment possibility in patients who are conscious, cooperative, breathing spontaneously, non-intubated and with stable cardiovascular status. Its appeal stems from potential utility in all resource settings, since it does not require complex devices or specialist critical care expertise to implement.

Conditional recommendation for

We suggest awake prone positioning for severely ill patients hospitalized with COVID-19 requiring supplemental oxygen (includes HFNO) or non-invasive ventilation *[Conditional recommendation for, moderate/low certainty evidence].*

Practical info

The GDG made a conditional recommendation for awake prone positioning in severely ill patients with COVID-19 requiring supplemental oxygen (including HFNO) or non-invasive ventilation.

Monitoring of patients and training of providers in caring for patients who are awake and prone, as part of multifaceted training for acute care management, are essential for implementation. Proning of severely ill and awake patients should be limited to those who do not have an immediate need for intubation due to concerns regarding airway protection, severe respiratory failure, or haemodynamic instability. In addition, patients being considered for proning should not be receiving non-invasive ventilation with high inflation pressures or be experiencing desaturation despite very high inspired oxygen concentrations. Patients for whom the safety of proning is considered borderline should be closely monitored. Supported side-lying can be considered in some patients as a reasonable alternative to full proning.

The optimal duration of proning was discussed by the panel, acknowledging that the median duration of proning received in the trials was 2.8 hours per day. This period was felt to be a reasonable target and noted that patients' motivation to turn prone and their and ability to turn supine in case of discomfort were important implementation considerations.

Resources:

1. https://www.who.int/publications/i/item/clinical-care-of-severe-acute-respiratory-infections-tool-kit

Ongoing uncertainties and opportunities for future research:

The GDG acknowledged remaining uncertainties regarding awake prone positioning that need to be addressed, including:

- discomfort that patients may experience during the intervention;
- treatment effects in specific subgroups, such as children and older persons;
- optimal duration of prone positioning;
- quantitative estimates of health system resources needed for awake prone positioning, compared with invasive mechanical ventilation;
- effectiveness of awake prone positioning for other infectious causes of acute respiratory failure not requiring immediate invasive mechanical ventilation.

Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

Twenty-one RCTs have addressed awake prone positioning for patients with COVID-19 not requiring invasive ventilation on supplemental oxygen. Awake prone positioning possibly reduces mortality (low certainty evidence) and probably reduces the need for invasive ventilation (moderate certainty evidence). Awake prone positioning possibly reduces ICU length of stay (low certainty evidence) and has little or no effect on hospital length of stay (high certainty evidence).

The possible harms of awake prone positioning are patient discomfort and pain, nausea, skin breakdown and dislodgement of vascular catheters. Inconsistent definitions and reporting precluded meta-analysis and formal GRADE assessment of these outcomes.

Certainty of the evidence

Low

For patient-important outcomes of mortality and the need for mechanical ventilation, the panel considered the direct evidence to be of low and moderate certainty, respectively. For mortality, the certainty of evidence was rated down twice due to imprecision because the confidence interval was consistent with both important benefit and important harm. For need for invasive ventilation, the confidence interval was consistent with both important benefit and unimportant benefit and was thus rated down once for imprecision. For the outcomes of ICU and hospital length of stay, the panel considered the direct evidence to be of low and high certainty, respectively. The certainty in the evidence was rated down once for inconsistency and once for imprecision for ICU length of stay.

Given the available direct randomized evidence, indirect evidence from non-COVID-19 populations was not used in this assessment.

Values and preferences

No substantial variability expected

The panel placed a relatively high value on a modest reduction in invasive mechanical ventilation, and, since patients experiencing discomfort would be able to return to the supine position, a lower value on the discomfort patients experience using awake prone positioning.

From a systems perspective, the panel also appreciated, on the one hand, the variable workload that awake prone positioning places on staff (particularly nurses) and, on the other hand, advantages from fewer patients needing invasive mechanical ventilation.

Resources and other considerations

Important issues, or potential issues not investigated

Patients who are able to follow instructions can often self-prone, without assistance from health care workers. Discomfort may arise in some circumstances; as these patients are awake, returning to the supine position would be a viable option. For patients who require assistance to be proned, personnel (primarily nurses) trained in the prone manoeuvre and in careful monitoring of patient respiratory status are required. The panel believed that this intervention should be feasible in all settings, but implementation requires resources for training and patient monitoring. The panel also believed that implementation of the intervention may be dependent on staffing requirements.

The panel also emphasized that there may be local cultural or contextual factors that may impact the implementation of prone positioning.

Justification

When moving from evidence to the conditional recommendation for the use of awake prone positioning in severely ill hospitalized patients with COVID-19 requiring supplemental oxygen, the panel emphasized the moderate certainty evidence of reduction in the need for invasive mechanical ventilation. It also noted the limited evidence of harm with widespread experience with this intervention across different resource settings thus far.

Subgroup analyses

No specific subgroups with a hypothesized direction of effect were highlighted by the panel.

Clinical question/ PICO

Population: Non-intubated patients with COVID-19 hypoxaemic respiratory failure
Intervention: Awake prone positioning + usual care
Comparator: No awake prone positioning

Summary

Data informing the Summary of Findings tables were extracted in an updated systematic review, available here *(571)*.

Outcome Timeframe	**Study results and measurements**	**Comparator** No awake prone positioning	**Intervention** Awake prone positioning + usual care	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality 8 Critical	Relative risk 0.93 (CI 95% 0.79 — 1.09) Based on data from 2,902 participants in 15 studies. (Randomized controlled)	**165** per 1000 Difference:	**154** per 1000 **12 fewer per 1000** (CI 95% 35 fewer — 15 more)	**Low** Due to very serious imprecision [1]	Awake prone position possibly reduces mortality
Endotracheal intubation 9 Critical	Relative risk 0.84 (CI 95% 0.74 — 0.94) Based on data from 3,008 participants in 17 studies. (Randomized controlled)	**256** per 1000 Difference:	**215** per 1000 **41 fewer per 1000** (CI 95% 67 fewer — 15 fewer)	**Moderate** Due to serious imprecision [2]	Awake prone position probably reduces endotracheal intubation
ICU Length of Stay 6 Important	Lower better Based on data from 2,293 participants in 12 studies. (Randomized controlled)	**10.3** (Mean) Difference:	**8.5** (Mean) **MD 1.78 lower** (CI 95% 3.81 lower — 0.24 higher)	**Low** Due to serious inconsistency and serious imprecision [3]	Awake prone positioning possibly reduces ICU length of stay
Hospital Length of Stay 6 Important	Lower better Based on data from 3,374 participants in 16 studies. (Randomized controlled)	**11.8** (Mean) Difference:	**11.6** (Mean) **MD 0 higher** (CI 95% 0.31 lower — 0.31 higher)	**High**	Awake prone positioning has little or no effect on hospital length of stay

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** The panel judged the confidence interval as consistent with both an important reduction in mortality and an important increase in mortality. **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The panel judged the confidence interval as consistent with both an important and an unimportant reduction in endotracheal intubation. **Publication bias: no serious.**
3. **Inconsistency: serious.** Inspection of the forest plots showed important variation in point estimated and non-overlapping CIs for some trials. **Indirectness: no serious. Imprecision: serious.** The 95% CI was consistent with large benefit (3.8 fewer days) and small harm (0.24 more days) . **Publication bias: no serious.**

3.4 Management of critical COVID-19: acute respiratory distress syndrome (ARDS)

The mortality in hospitalized and critically ill patients has varied substantially in different case series throughout the pandemic. The following recommendations are aligned with current international standards for management of all cause ARDS *(70)*.

3.4.1 Advanced non-invasive respiratory support

Info Box

What are advanced non-invasive respiratory support devices?

Broadly, these are devices that can provide respiratory support through their ability to provide higher oxygen flows or positive pressure or a combination of both. They are referred to as non-invasive as they do not involve the placement of a tube (e.g, endotracheal tube or tracheostomy tube) in the patient's airway (referred to as invasive approach).

There are three broad categories of devices that are referred to in our guidelines: high-flow nasal oxygen (HFNO); continuous positive airway pressure (CPAP); and non-invasive ventilation (NIV), also referred to as bilevel positive airway pressure (BiPAP). HFNO provides respiratory support predominantly through higher flows whereas CPAP and NIV provide support through a combination of higher flows and higher pressure.

Summary of recommendations (see sections below for additional details and in-depth explanation)

- In hospitalized patients with severe or critical COVID-19 and acute hypoxaemic respiratory failure (AHRF) not needing emergent intubation, we suggest high-flow nasal oxygen (HFNO) rather than standard oxygen therapy (SOT) (conditional recommendation).
- In hospitalized patients with severe or critical COVID-19 and acute hypoxaemic respiratory failure (AHRF) not needing emergent intubation, we suggest continuous positive airway pressure (CPAP) rather than standard oxygen therapy (SOT) (conditional recommendation).
- In hospitalized patients with severe or critical COVID-19 and acute hypoxaemic respiratory failure (AHRF) not needing emergent intubation, we suggest non-invasive ventilation (NIV) rather than standard oxygen therapy (SOT) (conditional recommendation).

The GDG chose not to make a recommendation regarding HFNO versus CPAP vs NIV due to the uncertainty of the data. Clinicians should therefore choose between the these devices on the basis of considerations such as availability of devices and the supply of oxygen, their personal comfort and experience, and patient-specific considerations (such as claustrophobia that some patients experience with CPAP masks, and nasal discomfort that some patients experience with HFNO).

3.4.1.1 High-flow nasal oxygen

Conditional recommendation for

In hospitalized patients with severe or critical COVID-19 and acute hypoxaemic respiratory failure (AHRF) not needing emergent intubation, we suggest high-flow nasal oxygen (HFNO) rather than standard oxygen therapy (SOT) *[Conditional recommendation, moderate certainty evidence].*

The GDG chose not to make a recommendation regarding high-flow nasal oxygen (HFNO) versus continuous positive airway pressure (CPAP) due to uncertainty of the data. Clinicians should therefore choose between the two on the basis of considerations such as availability of devices and the supply of oxygen, their personal comfort and experience, and patient-specific considerations (such as claustrophobia that some patients experience with CPAP masks, and nasal discomfort that some patients experience with HFNO).

The GDG elected to extend this recommendation to the paediatric age range (despite the absence of data), given the likely similar direction of benefit, but emphasized the need for more research in this population.

Practical info

There is no specific recommendation for the initial flow rate, FiO_2, or titration scheme. Based on clinical experience of the panel, initial flow rates of between 50 and 60 L/min and initial FiO_2 of 100% are suggested, titrated to patient SpO_2 and work of breathing. In children, a fixed rate of 2 L/min/kg of body weight is suggested.

For infection prevention precautions related to the use of these respiratory support devices, please refer to Section 5 on IPC. See also research needs.

Resources:

1. https://www.who.int/publications/i/item/clinical-care-of-severe-acute-respiratory-infections-tool-kit
2. https://openwho.org/courses/clinical-management-COVID-19-general-considerations
3. https://www.who.int/health-topics/oxygen#tab=tab_1

Evidence to decision

Benefits and harms	High-flow nasal oxygen, in comparison to standard oxygen therapy, may reduce mortality and need for invasive ventilation (direct PICO, low certainty evidence), probably reduces hospital length-of-stay and ICU length of stay (direct PICO, moderate certainty evidence) in patients with severe or critical COVID-19 experiencing AHRF but not requiring emergent intubation. Based on overall clinical experience with the device and its use among critically ill patients, the GDG was of the opinion that benefits are likely to supersede any potential harms.
Certainty of the evidence	**Comparisons with SOT:** Among trials in patients with AHRF and COVID-19, for the outcomes of mortality and need for invasive mechanical ventilation there is low certainty in the evidence, due to very serious imprecision. For the outcome of hospital length of stay and ICU length-of-stay, there is moderate certainty in the evidence, due to serious imprecision. Trials in non-COVID-19 ARDS provided low certainty evidence that high-flow nasal oxygen had little or no difference on mortality, compared with standard oxygen therapy, due to very serious imprecision. These trials also, however, also provided moderate certainty evidence of a decrease in the need for invasive mechanical ventilation and hospital length of stay. Effect on ICU length of stay was uncertain. **Comparisons between devices or interfaces:** Trials in patients with COVID-19 and AHRF provided very low certainty evidence for the comparison between HFNO and helmet NIV for outcomes of mortality, hospital length of stay, ICU length of stay due to extremely serious imprecision; whereas there is low certainty evidence for outcome of need for invasive ventilation due to very serious imprecision, and low certainty evidence for the outcome of device-related comfort due to serious risk of bias and serious imprecision. One trial in patients with COVID-19 and AHRF for the comparison of HFNO and CPAP provided very low certainty evidence for the outcome of mortality due to extremely serious imprecision. For the outcomes of need for invasive mechanical ventilation, hospital and ICU length of stay, the certainty of the evidence is low due to very serious imprecision. Trials in non-COVID-19 ARDS provided very low certainty evidence for the comparison of HFNO and face mask NIV on the outcomes of mortality and need for invasive mechanical ventilation due to a combination of serious indirectness, serious risk of bias and very serious or serious imprecision. For the outcome of ICU length of stay, the certainty of evidence is low due to very serious imprecision.
Values and preferences	Applying the agreed upon values and preferences, the GDG inferred that most well-informed patients with AHRF not requiring emergent intubation would choose to receive HFNO rather than standardoxygen therapy.
Resources and other considerations	Studies of HFNO, CPAP, and NIV were conducted in high-resource settings with ICUs, health care workers experienced in these interventions, and resources for patient monitoring and rescue in case of clinical deterioration. The GDG emphasized that implementation of any non-invasive respiratory support intervention requires consideration of the local context of oxygen supply, training of health care providers, additional equipment for patient monitoring, considerations around maintenance of equipment, cost, and organization of service delivery. Availability of these additional resources has traditionally been restricted to areas within hospitals that provide intensive care. The GDG believed that the availability of these additional resources should be expanded to facilitate safe delivery of non-invasive respiratory support interventions globally.

A specific consideration for HFNO is that these devices may require a higher oxygen flow compared with other non-invasive respiratory support devices. Appropriate calculations of oxygen needs should be made at the facility level when expanding clinical use of HFNO and other non-invasive respiratory devices.

Justification

When moving from evidence to the conditional recommendation for patients hospitalized for COVID-19 with AHRF and not requiring emergent intubation, the panel emphasized the low certainty of evidence from direct comparisons in patients with COVID-19 for the important outcomes of mortality and need for invasive mechanical ventilation. The GDG incorporated the indirect evidence from patients without COVID-19 and AHRF, which had moderate certainty evidence for reducing invasive mechanical ventilation and hospital length-of-stay.

The GDG integrated the available evidence on the risk to health care workers due to infection transmission with the use of high-flow nasal oxygen. There is currently insufficient evidence to inform recommendations for the outcome of health care worker transmission.

Choosing between devices:

The GDG chose not to make recommendations among non-invasive respiratory support devices because of the very low or low certainty of evidence and variable contextual factors of oxygen supply, staff training, and patient monitoring that would weigh more heavily in utilization decisions, compared with evidence of clinical effectiveness.

Research needs

Further research is needed about:

- Between-device comparisons such as between HFNO and CPAP;
- The impact of varying levels of positive pressure provided by these devices on evolving lung injury in patients with ARDS;
- The risks of aerosol generation and risk of transmission to HCWs based on choice of respiratory support device;
- Staffing requirements and skills in deploying these devices in resource-limited settings as well as on cost and oxygen requirements from the use of these devices;
- Specific populations such as children and pregnant women.

Clinical question/ PICO

Population: Hospitalized patients with severe or critical COVID-19 and AHRF not needing emergent intubation
Intervention: HFNO
Comparator: SOT

Summary

Evidence Summary

The meta-analysis for the comparison of HFNO vs SOT was informed by 4 RCTs *(74)(230)(75)(233)* which enrolled a total of 1053 participants* (direct PICO, i.e. COVID-19 patients with AHRF), and by 5 RCTs which enrolled a total of 1425 participants* (indirect PICO, i.e. non-COVID-19 ARDS patients) *(237)*. All the RCTs for the direct PICO were published. None of the trials evaluating the direct PICO included pregnant women or children. For the trials evaluating the indirect PICO, pregnant women and children were either excluded or there was no specific mention of their inclusion in methods or results sections of the trial *(237)*.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of HFNO compared with SOT for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

* Not all trials reported on all outcomes.

Outcome Timeframe	Study results and measurements	Comparator SOT	Intervention HFNO	Certainty of the evidence (Quality of evidence)	Summary
Mortality 9 Critical	Relative risk 0.87 (CI 95% 0.66 — 1.13) Based on data from 1,006 participants in 3 studies. (Randomized controlled)	**188** per 1000 Difference:	**164** per 1000 **24 fewer per 1000** (CI 95% 64 fewer — 24 more)	**Low** Due to very serious imprecision [1]	HFNO may decrease mortality
IMV 9 Critical	Relative risk 0.89 (CI 95% 0.77 — 1.03) Based on data from 1,053 participants in 3 studies. (Randomized controlled)	**417** per 1000 Difference:	**371** per 1000 **46 fewer per 1000** (CI 95% 96 fewer — 13 more)	**Low** Due to very serious imprecision [2]	HFNO may decrease IMV
Hospital LOS 9 Critical	Lower better Based on data from 1,003 participants in 3 studies. (Randomized controlled)	**16.28** days (Mean) Difference:	**14.92** days (Mean) **MD 1.08 fewer** (CI 95% 2.48 fewer — 0.35 more)	**Moderate** Due to serious imprecision [3]	HFNO probably decreases hospital LOS
ICU LOS 6 Important	Lower better Based on data from 1,003 participants in 3 studies. (Randomized controlled)	**5.83** days (Mean) Difference:	**4.65** days (Mean) **MD 0.77 fewer** (CI 95% 1.45 fewer — 0.08 fewer)	**Moderate** Due to serious imprecision [4]	HFNO probably has little or no difference on ICU LOS

1, 2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence interval that includes important benefit and harm. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence interval that includes benefit and harm. **Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**

Clinical question/ PICO

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: HFNO
Comparator: SOT

Summary

The meta-analysis for the comparison of HFNO vs SOT was informed by 4 RCTs *(74)(230)(75)(233)*, which enrolled a total of 1053 participants* (direct PICO, i.e. COVID-19 patients with AHRF) and by 5 RCTs which enrolled a total of 1425 participants* (indirect PICO, i.e. non-COVID ARDS patients) *(237)*. All the RCTs for the direct PICO were published. None of the trials evaluating the direct PICO included pregnant women or children. For the trials evaluating the indirect PICO, pregnant women and children were either excluded or there was no specific mention of their inclusion in methods or in the results sections *(237)*.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of HFNO compared with SOT for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

* Not all trials reported on all outcomes.

Outcome Timeframe	**Study results and measurements**	**Comparator** SOT	**Intervention** HFNO	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality [1] 9 Critical	Relative risk 0.98 (CI 95% 0.83 — 1.15) Based on data from 1,344 participants in 4 studies. (Randomized controlled)	**291** per 1000 Difference:	**285** per 1000 **6 fewer per 1000** (CI 95% 49 fewer — 44 more)	**Low** Due to very serious imprecision [2]	HFNO may have little or no difference on mortality
IMV 9 Critical	Relative risk 0.74 (CI 95% 0.56 — 0.99) Based on data from 668 participants in 4 studies. (Randomized controlled)	**207** per 1000 Difference:	**153** per 1000 **54 fewer per 1000** (CI 95% 91 fewer — 2 fewer)	**Moderate** Due to serious imprecision [3]	HFNO probably decreases IMV
Hospital LOS 9 Critical	Lower better Based on data from 998 participants in 2 studies. (Randomized controlled)	**16.26** days (Median) Difference:	**14.46** days (Median) **MD 1.17 fewer** (CI 95% 3.16 fewer — 0.83 more)	**Moderate** Due to serious imprecision [4]	HFNO probably decreases hospital LOS
ICU LOS 6 Important	Based on data from 996 participants in 2 studies. (Randomized controlled)			**Very low** Due to extremely serious inconsistency [5]	We are very uncertain of the impact of HFNO on ICU LOS

1. Longest duration mortality data available, includes mix of hospital and end of study (EOS) outcomes
2. **Inconsistency: no serious.** The magnitude of statistical heterogeneity was moderate, with I^2: 44%. **Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals that include important benefit and harm. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Number of patients does not meet the optimal information size. **Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence interval. **Publication bias: no serious.**
5. **Inconsistency: very serious.** The magnitude of statistical heterogeneity was high, with I^2: 85%, the direction of the effect is not consistent between the included studies. One RCT suggested large benefit while one RCT suggested large harm (rated down by three). **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

3.4.1.2 Continuous positive airway pressure (CPAP)

Conditional recommendation for

In hospitalized patients with severe or critical COVID-19 and AHRF not needing emergent intubation, we suggest CPAP, rather than standard oxygen therapy *[Conditional recommendation, moderate certainty evidence].*

The GDG chose not to make a recommendation regarding optimal interface for CPAP, whether helmet or face mask, given the lack of direct data available for the comparison. The choice between interface should be guided by clinician experience, availability, and patient comfort.

The GDG chose not to make a recommendation regarding HFNO versus CPAP due to the uncertainty of the data. Clinicians should choose between the three on the basis of considerations such as availability of devices and the local supply of oxygen, their personal comfort and experience with the relevant devices, and patient-specific considerations (such as claustrophobia that some patients experience with CPAP/NIV masks, and nasal discomfort that some patients experience with HFNO).

Given the likely similar direction of benefit, the GDG chose to extend this recommendation to the paediatric age range (despite the absence of data), while emphasizing the need for more research in this population.

Practical info

There is no specific recommendation as to the initial pressure to be used for CPAP, leaving to local clinical decision-making and patient-specific factors. Based on clinical experience of the GDG, there is a suggestion to start with a pressure of 5–10 cm H_2O, titrated to patient comfort and work of breathing, with FiO_2 titrated to achieve the target oxygen saturation when using facemask or oral-nasal mask. For use of helmet interfaces, additional information can be found in recent publications *(355)*.

For infection prevention precautions related to the use of these respiratory support devices, please refer to Chapter 5 on IPC. See also Research needs.

Resources:

1. https://www.who.int/publications/i/item/clinical-care-of-severe-acute-respiratory-infections-tool-kit
2. https://openwho.org/courses/clinical-management-COVID-19-general-considerations
3. https://www.who.int/health-topics/oxygen#tab=tab_1

Evidence to decision

Benefits and harms	In patients with severe or critical COVID-19 and AHRF not requiring emergent intubation, CPAP, in comparison with standard oxygen therapy, may decrease mortality (direct PICO, low certainty evidence), probably decreases the need for invasive mechanical ventilation (direct PICO, moderate certainty evidence), may decrease hospital length-of-stay (direct PICO, low certainty evidence), and may have little or no impact on ICU length-of-stay (direct PICO, low certainty evidence). Based on overall clinical experience with the device and its use among critically ill patients, the GDG was of the opinion that benefits are likely to supersede any potential harms.
Certainty of the evidence	**Comparisons with SOT:** In the direct population of patients with severe or critical COVID-19 experiencing acute hypoxaemic respiratory failure but not requiring emergent intubation, for the outcome of mortality, there is low-certainty evidence due to very serious imprecision. For the outcome of need for invasive mechanical ventilation, there is moderate certainty evidence due to serious imprecision. For the outcomes of ICU and hospital length-of-stay, there is low certainty evidence, due to very serious imprecision. In the indirect population of patients with non-COVID-19 ARDS, there were studies evaluating both helmet CPAP and face mask CPAP, compared with standard oxygen therapy, largely with very low certainty evidence due to extremely serious imprecision.

Comparison between devices or interfaces:

One trial in patients with COVID-19 and AHRF for the comparison of CPAP and HFNO provided very low certainty evidence for the outcome of mortality due to extremely serious imprecision. For the outcomes of need for invasive mechanical ventilation, hospital and ICU length of stay, the certainty of the evidence is low due to very serious imprecision.

Values and preferences

Applying the agreed upon values and preferences, the GDG inferred that most well-informed patients with AHRF not requiring emergent intubation would choose to receive CPAP rather than standard oxygen therapy.

Resources and other considerations

Studies of HFNO, CPAP, and NIV were conducted in high-resource settings with ICUs, health care workers experienced in these interventions, and resources for patient monitoring and rescue in case of clinical deterioration. The GDG emphasized that implementation of any non-invasive respiratory support intervention requires consideration of the local context of oxygen supply, training of health care providers, additional equipment for patient monitoring, considerations around maintenance of equipment, cost, and organization of service delivery. Availability of these additional resources has traditionally been restricted to areas within hospitals that provide intensive care. The GDG believed that the availability of these additional resources should be expanded to facilitate safe delivery of non-invasive respiratory support interventions globally.

Justification

When moving from evidence to the conditional recommendation for patients hospitalized for COVID-19 with acute hypoxaemic respiratory failure not requiring emergent intubation, the panel noted the low certainty of evidence for the important outcomes of mortality, but the moderate certainty for reduction in the need for invasive mechanical ventilation. The panel incorporated indirect evidence from patients without COVID-19, but acknowledged the largely very low certainty in that evidence.

Choosing between devices:

For the direct comparison of CPAP with high-flow nasal oxygen, the GDG noted the very low certainty evidence for the important outcome of mortality. The low certainty in the available evidence that CPAP, when compared with high-flow nasal oxygen, decreases the requirement for invasive mechanical ventilation also influenced the decision-making, and the panel felt that more evidence was required to make a recommendation for this comparison.

The panel integrated the available evidence on the risk to health care workers due to infection transmission with the use of CPAP. There is currently insufficient evidence to inform recommendations for the outcome of health care worker transmission.

Research needs

Further research is needed about:

- The optimal choice of interface while delivering CPAP (helmet vs face mask, etc);
- Between-device comparisons such as between HFNO and CPAP;
- The impact of varying levels of positive pressure provided by these devices on evolving lung injury in patients with ARDS;
- The risks of aerosol generation and risk of transmission to health care workers based on choice of respiratory support device;
- Staffing requirements and skills in deploying these devices in resource-limited settings as well as on cost and oxygen requirements from the use of these devices;
- Specific populations such as children and pregnant women.

Clinical question/ PICO

Population: Hospitalized patients with severe or critical COVID-19 and AHRF not needing emergent intubation
Intervention: CPAP
Comparator: SOT

Summary

The meta-analysis for the comparison of CPAP vs SOT was informed by the results of one trial which enrolled 742 participants* (direct PICO, i.e. COVID-19 patients with AHRF) *(233)*, by 3 RCTs which enrolled a total of 168 patients* (Helmet CPAP vs SOT; indirect PICO, i.e. non-COVID patients with ARDS) *(237)* and by one additional trial that enrolled 123 patients* (face mask CPAP vs SOT; indirect PICO, i.e. non-COVID patients with ARDS) *(237)*. The trial that informed the direct PICO was published. None of the trials evaluating the direct PICO included pregnant women or children. For the trials evaluating the indirect PICO, pregnant women and children were either excluded or there was no specific mention of their inclusion in methods or results sections of the trial *(237)*.

For patien with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of CPAP compared with SOT for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

* Not all trials reported on all outcomes.

Note: for RECOVERY-RS (direct PICO- COVID-19 patients with AHRF), the denominator number of patients varied by outcome.

Outcome Timeframe	**Study results and measurements**	**Comparator** SOT	**Intervention** CPAP	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality 9 Critical	Relative risk 0.87 (CI 95% 0.64 — 1.18) Based on data from 737 participants in 1 studies. (Randomized controlled)	**192** per 1000 Difference:	**167** per 1000 **25 fewer per 1000** (CI 95% 69 fewer — 35 more)	**Low** Due to very serious imprecision [1]	CPAP may decrease mortality
IMV 9 Critical	Relative risk 0.81 (CI 95% 0.67 — 0.98) Based on data from 733 participants in 1 studies. (Randomized controlled)	**413** per 1000 Difference:	**335** per 1000 **78 fewer per 1000** (CI 95% 136 fewer — 8 fewer)	**Moderate** Due to serious imprecision [2]	CPAP probably decreases IMV
Hospital LOS 9 Critical	Lower better Based on data from 737 participants in 1 studies. (Randomized controlled)	**17.3** days (Mean) Difference:	**16.4** days (Mean) **MD 0.96 fewer** (CI 95% 3.59 fewer — 1.67 more)	**Low** Due to very serious imprecision [3]	CPAP may decrease hospital LOS
ICU LOS 6 Important	Lower better Based on data from 737 participants in 1 studies. (Randomized controlled)	**9.6** days (Mean) Difference:	**9.5** days (Mean) **MD 0.08 fewer** (CI 95% 2.23 fewer — 2.07 more)	**Low** Due to very serious imprecision [4]	CPAP may have little or no difference on ICU LOS

1, 3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Data from one study, wide confidence interval that includes important benefit and harm. **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Data from one study, number of patients does not meet the optimal information size. **Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Data from one study, wide confidence interval that includes benefit and harm. **Publication bias: no serious.**

Clinical question/ PICO

Population: Hospitalized patients with severe or critical COVID-19 and AHRF not needing emergent intubation
Intervention: CPAP
Comparator: HFNO

Summary

One RCT enrolled a total of 1273 participants into SOT, HFNO and CPAP arms *(233)*, but did not directly compare CPAP with HFNO and so the meta-analysis for the comparison of CPAP vs HFNO was informed by an indirect comparison of 793 participants (direct PICO, i.e. COVID-19 patients with AHRF). The RCT for the direct PICO is published and did not include children or pregnant women.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of CPAP vs HFNO for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO	**Intervention** CPAP	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality [1] 9 Critical	Relative risk 0.95 (CI 95% 0.52 — 1.71) Based on data from 793 participants in 1 studies. (Randomized controlled)	**188** per 1000 Difference:	**179** per 1000 **9 fewer per 1000** (CI 95% 90 fewer — 133 more)	**Very low** Due to extremely serious imprecision [2]	We are very uncertain of the impact of CPAP on mortality
IMV 9 Critical	Relative risk 0.69 (CI 95% 0.43 — 1.09) Based on data from 791 participants in 1 studies. (Randomized controlled)	**411** per 1000 Difference:	**284** per 1000 **127 fewer per 1000** (CI 95% 234 fewer — 37 more)	**Low** Due to very serious imprecision [3]	CPAP may decrease IMV
Hospital LOS	Lower better Based on data from 791 participants in 1 studies. (Randomized controlled)	**18.3** days (Mean) Difference:	**16.4** days (Mean) **MD 1.67 fewer** (CI 95% 5.43 fewer — 2.09 more)	**Low** Due to very serious imprecision [4]	CPAP may decrease hospital LOS
ICU LOS 6 Important	Lower better Based on data from 791 participants in 1 studies. (Randomized controlled)	**10.5** days (Mean) Difference:	**9.5** days (Mean) **MD 1.02 fewer** (CI 95% 3.97 fewer — 1.93 more)	**Low** Due to very serious imprecision [5]	CPAP may decrease ICU LOS

1. For this outcome, mortality is at 30d
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** Data from one study, Wide confidence interval that includes important large benefit and harm (rated down by three). **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Data from one study, wide confidence interval that includes moderate benefit and harm. **Publication bias: no serious.**

4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Data from one study, wide confidence intervals that include important benefit and harm.
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Data from one study, Wide confidence interval that includes important benefit and harm, . **Publication bias: no serious.**

Clinical question/ PICO

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: Helmet CPAP
Comparator: SOT

Summary

The meta-analysis for the comparison of CPAP vs SOT was informed by the results of one trial which enrolled 742 participants* (direct PICO, i.e. COVID-19 patients with AHRF) *(233)*, by 3 RCTs which enrolled a total of 168 patients* (helmet CPAP vs SOT; indirect PICO, i.e. non-COVID patients with ARDS) *(237)* and by one additional trial that enrolled 123 patients* (face mask CPAP vs SOT; indirect PICO, i.e. non-COVID patients with ARDS) *(237)*. The trial that informed the direct PICO was published. None of the trials evaluating the direct PICO included pregnant women or children. For the trials evaluating the indirect PICO, pregnant women and children were either excluded or there was no specific mention of their inclusion in methods or results sections of the trial *(237)*.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of CPAP compared with SOT for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

* Not all trials reported on all outcomes.

Note: for RECOVERY-RS (direct PICO- COVID-19 patients with AHRF), the denominator number of patients varied by outcome.

Outcome Timeframe	**Study results and measurements**	**Comparator** SOT	**Intervention** Helmet CPAP	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality 9 Critical	Relative risk 0.23 (CI 95% 0.1 — 0.55) Based on data from 168 participants in 3 studies. (Randomized controlled)	**250** per 1000 Difference:	**58** per 1000 **192 fewer per 1000** (CI 95% 225 fewer — 112 fewer)	**Very low** Due to serious indirectness and very serious imprecision [1]	We are very uncertain of the impact of helmet CPAP on mortality
IMV 9 Critical	Relative risk 0.45 (CI 95% 0.15 — 1.34) Based on data from 168 participants in 3 studies. (Randomized controlled)	**102** per 1000 Difference:	**46** per 1000 **56 fewer per 1000** (CI 95% 87 fewer — 35 more)	**Very low** Due to serious indirectness and very serious imprecision [2]	We are very uncertain of the impact of helmet CPAP on IMV
Hospital LOS 9 Critical	Lower better Based on data from 81 participants in 1 studies. (Randomized controlled)	**14** days (Median) Difference:	**14.5** days (Median) **MD 0.5 more** (CI 95% 3.75 fewer — 4.75 more)	**Low** Due to very serious imprecision [3]	Helmet CPAP may have little or no difference on hospital LOS

Outcome Timeframe	Study results and measurements	Comparator SOT	Intervention Helmet CPAP	Certainty of the evidence (Quality of evidence)	Summary
ICU LOS 6 Important					No studies were found that looked at ICU LOS

1. **Risk of Bias: no serious.** One trial stopped earlier than scheduled, potential for overestimating benefits. **Inconsistency: no serious. Indirectness: serious.** One of three RCTs was in patients with hematologic malignancies. **Imprecision: very serious.** Number of patients is far less than would be required to meet the optimal information size (<25%). **Publication bias: no serious.**
2. **Inconsistency: no serious.** The magnitude of statistical heterogeneity was high, with I^2: 64%. **Indirectness: serious.** One of three RCTs in patients with hematologic malignancies. **Imprecision: very serious.** Wide confidence interval that includes important benefit and harm. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Data from one study, wide confidence interval that includes important benefits and harms. **Publication bias: no serious.**

Clinical question/ PICO

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: Face mask CPAP
Comparator: SOT

Summary

The meta-analysis for the comparison of CPAP vs SOT was informed by the results of one trial which enrolled 742 participants* (direct PICO, i.e. COVID-19 patients with AHRF) *(233)*, by 3 RCTs which enrolled a total of 168 patients* (helmet CPAP vs SOT; indirect PICO, i.e. non-COVID patients with ARDS) *(237)* and by one additional trial that enrolled 123 patients* (face mask CPAP vs SOT; indirect PICO, i.e. non-COVID patients with ARDS) *(237)*. The trial that informed the direct PICO was published. None of the trials evaluating the direct PICO included pregnant women or children. For the trials evaluating the indirect PICO, pregnant women and children were either excluded or there was no specific mention of their inclusion in methods or results sections of the trial *(237)*.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of CPAP compared with SOT for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

* Not all trials reported on all outcomes.

Note: for RECOVERY-RS (direct PICO- COVID-19 patients with AHRF), the denominator number of patients varied by outcome.

Outcome Timeframe	Study results and measurements	Comparator SOT	Intervention Face mask CPAP	Certainty of the evidence (Quality of evidence)	Summary
Mortality 9 Critical	Relative risk 0.71 (CI 95% 0.38 — 1.32) Based on data from 123 participants in 1 studies. (Randomized controlled)	**295** per 1000 Difference:	**209** per 1000 **86 fewer per 1000** (CI 95% 183 fewer — 94 more)	**Very low** Due to extremely serious imprecision [1]	We are very uncertain of the impact of face mask CPAP on mortality
IMV 9 Critical	Relative risk 0.86 (CI 95% 0.54 — 1.37) Based on data from 123 participants in 1 studies.	**393** per 1000	**338** per 1000	**Very low** Due to extremely serious imprecision [2]	We are very uncertain of the impact of face mask CPAP on IMV

Outcome Timeframe	Study results and measurements	Comparator SOT	Intervention Face mask CPAP	Certainty of the evidence (Quality of evidence)	Summary
	(Randomized controlled)	Difference:	**55 fewer per 1000** (CI 95% 181 fewer — 145 more)		
Hospital LOS 9 Critical	Lower better Based on data from 81 participants in 1 studies. (Randomized controlled)	**16** days (Median) Difference:	**14** days (Median) **MD 2 fewer** (CI 95% 17.5 fewer — 13.5 more)	**Very low** Due to extremely serious imprecision [3]	We are very uncertain of the impact of face mask CPAP on hospital LOS
ICU LOS 6 Important	Lower better Based on data from 81 participants in 1 studies. (Randomized controlled)	**9** days (Median) Difference:	**9** days (Median) **MD 0 fewer** (CI 95% 8.89 fewer — 8.89 more)	**Very low** Due to extremely serious imprecision [4]	We are very uncertain of the impact of face mask CPAP on ICU LOS

1, 2, 3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** Data from one study, wide confidence intervals that include important large benefit and harm (rated down by three). **Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** Data from one study, wide confidence intervals that include important large benefit and harm (rated down by three levels). **Publication bias: no serious.**

3.4.1.3 Non-invasive ventilation (NIV)

Conditional recommendation for

In hospitalized patients with severe or critical COVID-19 and AHRF not needing emergent intubation, we suggest non-invasive ventilation, rather than standard oxygen therapy *[Conditional recommendation, moderate certainty evidence].*

The GDG chose not to make a recommendation regarding optimal interface for NIV, whether helmet or face mask, given the limited data. The choice between interface should be guided by clinician experience, availability, and patient comfort.

The GDG chose not to make a recommendation regarding HFNO versus CPAP versus NIV due to the uncertainty of the data. Clinicians should choose on the basis of considerations such as availability of devices and the supply of oxygen, their personal comfort and experience, and patient-specific considerations (such as claustrophobia that some patients experience with CPAP/ NIV masks, and nasal discomfort that some patients experience with HFNO).

Given the likely similar direction of benefit, the GDG elected to extend this recommendation to the paediatric age range (despite the absence of randomized trial data), while emphasizing the need for more research in this population.

Practical info

There is no specific recommendation for the initial settings to be used for non-invasive ventilation, with local experience and patient-specific factors informing decisions and manufacturer instructions. Based on clinical experience of the GDG, there is a suggestion to start with an expiratory positive airway pressure of 5–10 cmH_2O, an inspiratory positive airway pressure to achieve a tidal volume of ~6 ml/kg, titration of both settings to patient comfort and work of breathing, and titration of FiO_2 to achieve the target oxygen saturation when using facemask or oral-nasal mask. For use of helmet interfaces, additional information can be found in recent publications *(235)*.

For infection prevention precautions related to the use of these respiratory support devices, please refer to Chapter 5 on IPC. See also Research needs.

Resources:

1. https://www.who.int/publications/i/item/clinical-care-of-severe-acute-respiratory-infections-tool-kit
2. https://openwho.org/courses/clinical-management-COVID-19-general-considerations
3. https://www.who.int/health-topics/oxygen#tab=tab_1

Evidence to decision

Benefits and harms	In patients with non-COVID-19 ARDS, face mask NIV probably reduces mortality (indirect PICO, moderate certainty) and need for invasive mechanical ventilation when compared to standard oxygen therapy. Based on overall clinical experience with the device and its use among critically ill patients, the GDG was of the opinion that benefits are likely to supersede any potential harms.
Certainty of the evidence	**Comparisons with SOT:** No trials enrolling patients with COVID-19 are available. In the indirect population of hospitalized patients with ARDS not due to COVID-19 and not needing emergent intubation, moderate certainty evidence (due to serious indirectness) suggests that face mask NIV probably reduces mortality compared with SOT, and moderate-certainty evidence (due to serious inconsistency) suggests that NIV probably reduces the need for invasive mechanical ventilation. Very low-certainty evidence (due to serious inconsistency, serious imprecision, and serious indirectness) suggests impact of NIV on hospital and ICU length of stay is uncertain **Comparisons between devices or interfaces:** Trials in patients with COVID-19 and AHRF provided very low certainty evidence for the comparison between helmet NIV and HFNO for outcomes of mortality, hospital length of stay, ICU length of stay due to extremely serious imprecision; whereas there is low certainty evidence for outcome of need for invasive ventilation due to very serious imprecision, and low certainty evidence for the outcome of device-related comfort due to serious risk of bias and serious imprecision. Trials in patients with non-COVID-19 ARDS provided very low certainty evidence for the comparison between face mask NIV and HFNO for the outcomes of mortality and need for invasive ventilation due to serious indirectness, serious risk of bias and serious and very serious imprecision. For the outcome of ICU length of stay, the certainty of evidence is low due to very serious imprecision. Trials in patients with non-COVID-19 ARDS provided low certainty evidence for the comparison between helmet NIV and face mask NIV for the outcomes of mortality, need for invasive mechanical ventilation and hospital length of stay due to very serious imprecision.
Values and preferences	Applying the agreed upon values and preferences, the GDG inferred that most well-informed patients with AHRF not requiring emergent intubation would choose to receive NIV rather than standard oxygen therapy.
Resources and other considerations	Studies of HFNO, CPAP, and NIV were conducted in high-resource settings with ICUs, health care workers experienced in these interventions, and resources for patient monitoring and rescue in case of clinical deterioration. The GDG emphasized that implementation of any non-invasive respiratory support intervention requires consideration of the local context of oxygen supply, training of health care providers, additional equipment for patient monitoring, considerations around maintenance of equipment, cost, and organization of service delivery. Availability of these additional resources has traditionally been restricted to areas within hospitals that provide intensive care. The GDG believed that the availability of these additional resources should be expanded to facilitate safe delivery of non-invasive respiratory support interventions globally.

Justification

When moving from evidence to the conditional recommendation for patients hospitalized for COVID-19 with acute hypoxaemic respiratory failure and not requiring emergent intubation, the panel emphasized the moderate certainty of evidence from indirect comparisons in patients without COVID-19 for the important outcomes of mortality and need for invasive mechanical ventilation.

The GDG integrated the available evidence on the risk to health care workers due to infection transmission with the use of non-invasive ventilation. There is currently insufficient evidence to inform recommendations for the outcome of health care worker transmission.

The GDG chose not to make recommendations among non-invasive respiratory support devices because of the very low or low certainty of evidence and variable contextual factors of oxygen supply, staff training, and patient monitoring that would weigh more heavily in utilization decisions, compared with evidence of clinical effectiveness.

Research needs

Further research is needed about:

- The optimal choice of interface while delivering CPAP (helmet vs face mask, etc);
- Between-device comparisons such as between HFNO and CPAP;
- The impact of varying levels of positive pressure provided by these devices on evolving lung injury in patients with ARDS;
- The risks of aerosol generation and risk of transmission to health care workers based on choice of respiratory support device;
- Staffing requirements and skills in deploying these devices in resource-limited settings as well as on cost and oxygen requirements from the use of these devices;
- Specific populations such as children and pregnant women.

Clinical question/ PICO

Population: Hospitalized patients with severe or critical COVID-19 and AHRF not needing emergent intubation

Intervention: Helmet NIV

Comparator: HFNO

Summary

The meta-analysis for the comparison for Helmet NIV vs HFNO was informed by the results of one trial which enrolled 110 patients (direct PICO, i.e. COVID-19 patients with AHRF) *(235)*. The trial was published and did not include children or pregnant women.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of Helmet NIV vs HFNO for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO	**Intervention** Helmet NIV	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality [1] At 60 days 9 Critical	Relative risk 1.1 (CI 95% 0.55 — 2.2) Based on data from 110 participants in 1 studies. (Randomized controlled)	**236** per 1000 Difference:	**260** per 1000 **24 more per 1000** (CI 95% 106 fewer — 283 more)	**Very low** Due to extremely serious imprecision [2]	We are very uncertain of the impact of helmet NIV on mortality
IMV 9 Critical	Relative risk 0.54 (CI 95% 0.32 — 0.89) Based on data from 110 participants in 1 studies. (Randomized controlled)	**509** per 1000 Difference:	**275** per 1000 **234 fewer per 1000** (CI 95% 346 fewer — 56 fewer)	**Low** Due to very serious imprecision [3]	Helmet NIV may decrease IMV

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO	**Intervention** Helmet NIV	**Certainty of the evidence** (Quality of evidence)	**Summary**
Hospital LOS 9 Critical	Lower better Based on data from 110 participants in 1 studies. (Randomized controlled)	**22** days (Median) Difference:	**21** days (Median) **MD 1 fewer** (CI 95% 9.2 fewer — 7.2 more)	**Very low** Due to extremely serious imprecision [4]	We are very uncertain of the impact of helmet NIV on hospital LOS
ICU LOS 6 Important	Lower better Based on data from 110 participants in 1 studies. (Randomized controlled)	**10** days (Median) Difference:	**9** days (Median) **MD 1 fewer** (CI 95% 6.2 fewer — 7.3 more)	**Very low** Due to extremely serious imprecision [5]	We are very uncertain of the impact of helmet NIV on ICU LOS
Device-related discomfort 6 Important	Lower better Based on data from 110 participants in 1 studies. (Randomized controlled)	**1.8** VAS points (Mean) Difference:	**3.7** VAS points (Mean) **MD 1.9 higher** (CI 95% 1.4 higher — 2.5 higher)	**Low** Due to serious risk of bias and serious imprecision [6]	Helmet NIV may increase device-related discomfort

1. For this outcome, mortality is at 60d
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** Data from one study, wide confidence intervals that include important large benefit and harm (rated down by three). **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Data from one study, large and implausible effect, number of patients does not meet the optimal information size. **Publication bias: no serious.**
4, 5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** Data from one study, wide confidence interval that includes important large benefit and harm (rated down by three). **Publication bias: no serious.**
6. **Risk of Bias: serious.** Post hoc outcome assessment, multiple time points collected but not reported. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Data from one study, number of patients is far less than would be required to meet the optimal information size (<20%). **Publication bias: no serious.**

Clinical question/ PICO

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: Facemask NIV
Comparator: SOT

Summary

The meta-analysis for the comparison of face mask NIV vs SOT was informed by 11 RCTs that enrolled 1254 participants* (indirect PICO, i.e. non COVID patients with ARDS) *(237)*. All RCTs were published and trials either explicitly excluded pregnant women or children or did not mention them in their methods or results sections.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of face mask NIV vs SOT for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

* Not all trials reported on all outcomes.

Outcome Timeframe	Study results and measurements	Comparator SOT	Intervention Facemask NIV	Certainty of the evidence (Quality of evidence)	Summary
Mortality 9 Critical	Relative risk 0.83 (CI 95% 0.71 — 0.96) Based on data from 1,254 participants in 11 studies. (Randomized controlled)	**347** per 1000 Difference:	**288** per 1000 **59 fewer per 1000** (CI 95% 101 fewer — 14 fewer)	**Moderate** Due to serious indirectness [1]	Face mask NIV probably decreases mortality
IMV 9 Critical	Relative risk 0.74 (CI 95% 0.64 — 0.86) Based on data from 1,166 participants in 10 studies. (Randomized controlled)	**416** per 1000 Difference:	**308** per 1000 **108 fewer per 1000** (CI 95% 150 fewer — 58 fewer)	**Moderate** Due to serious inconsistency [2]	Face mask NIV probably decreases IMV
Hospital LOS 9 Critical	Lower better Based on data from 829 participants in 6 studies. (Randomized controlled)	**20.51** days (Median) Difference:	**17.93** days (Median) **MD 2.02 fewer** (CI 95% 4.39 fewer — 0.35 more)	**Low** Due to serious inconsistency and serious imprecision [3]	Face mask NIV may decrease hospital LOS
ICU LOS 6 Important	Lower better Based on data from 1,152 participants in 10 studies. (Randomized controlled)	**9.43** days (Median) Difference:	**7.85** days (Median) **MD 1.61 fewer** (CI 95% 3.21 fewer — 0.03 fewer)	**Low** Due to serious inconsistency and serious imprecision [4]	Face mask NIV may decrease ICU LOS

1. **Inconsistency: no serious. Indirectness: serious.** RCT populations include immunocompromised, stem cell or solid organ transplant, severe thoracic trauma, mixed community-acquired pneumonia and AHRF patients. **Imprecision: no serious.** 1.4% is considered an important reduction in mortality. **Publication bias: no serious.**
2. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 57%. **Indirectness: no serious.** RCT populations include immunocompromised, stem cell or solid organ transplant, mixed community-acquired pneumonia and AHRF patients. **Imprecision: no serious. Publication bias: no serious.**
3. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2:55%. **Indirectness: no serious. Imprecision: serious.** Wide confidence interval that includes benefit and harm. **Publication bias: no serious.**
4. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 75%. **Indirectness: no serious. Imprecision: serious.** Wide confidence interval that includes benefit and harm. **Publication bias: no serious.**

Clinical question/ PICO

Population: Hospitalized patients with ARDS and AHRF who do not need emergent intubation
Intervention: Face mask NIV
Comparator: HFNO

Summary

The meta-analysis for the comparison of face mask NIV vs HFNO was informed by 3 RCTs that enrolled 316 participants* (indirect PICO, i.e. non COVID patients with ARDS) *(237)*. All trials were published and either explicitly excluded pregnant women and children or did not mention their inclusion in the methods and results section.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of face mask NIV compared with HFNO for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

* Not all trials reported all outcomes.

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO	**Intervention** Face mask NIV	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality 9 Critical	Relative risk 1.83 (CI 95% 1.15 — 2.89) Based on data from 286 participants in 2 studies. (Randomized controlled)	**157** per 1000 Difference:	**287** per 1000 **130 more per 1000** (CI 95% 24 more — 297 more)	**Very low** Due to serious indirectness and very serious imprecision [1]	We are very uncertain of the impact of face mask NIV on mortality
IMV 9 Critical	Relative risk 1.22 (CI 95% 0.94 — 1.59) Based on data from 316 participants in 3 studies. (Randomized controlled)	**364** per 1000 Difference:	**444** per 1000 **80 more per 1000** (CI 95% 22 fewer — 215 more)	**Very low** Due to serious risk of bias, serious imprecision, and serious indirectness [2]	We are very uncertain of the impact of face mask NIV on IMV
Hospital LOS 9 Critical	Lower better		CI 95%		No studies were found that looked at hospital LOS
ICU LOS 6 Important	Lower better Based on data from 216 participants in 1 studies. (Randomized controlled)	**12.8** days (Median) Difference:	**13.35** days (Median) **MD 0.55 more** (CI 95% 3.16 fewer — 4.26 more)	**Low** Due to very serious imprecision [3]	Face mask NIV may have little or no difference on ICU LOS

1. **Inconsistency: no serious.** The magnitude of statistical heterogeneity was moderately high, with I^2: 51%. **Indirectness: serious.** Differences between the population of interest and those studied (one of two RCTs 100% in interstitial lung disease patients, the other 100% with community-acquired pneumonia). **Imprecision: very serious.** Number of patients is far less than would be required to meet the optimal information size. **Publication bias: no serious.**
2. **Risk of Bias: serious.** Two of three trials have unclear sequence generation and concealment of allocation during randomization process (one is a research abstract with incomplete data). **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied (one of three RCTs 100% in interstitial lung disease patients, one reports 100% with community-acquired pneumonia, and a third reports mixed acute respiratory failure and community-acquired pneumonia). **Imprecision: serious.** Wide confidence interval contains important benefit and harm. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals that include benefit and harm. Data from one study. **Publication bias: no serious.**

Clinical question/ PICO

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: Helmet NIV
Comparator: Face mask NIV

Summary

The meta-analysis for the comparison of helmet NIV vs face mask NIV was informed by one trial that enrolled 83 participants (indirect PICO, i.e. non COVID patients with ARDS) *(237)*. The trial was published and did not include pregnant women or children.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of helmet NIV compared with face mask NIV for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

Outcome Timeframe	**Study results and measurements**	**Comparator** Face mask NIV	**Intervention** Helmet NIV	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality [1] 9 Critical	Relative risk 0.6 (CI 95% 0.37 — 0.99) Based on data from 83 participants in 1 studies. (Randomized controlled)	**564** per 1000 Difference:	**338** per 1000 **226 fewer per 1000** (CI 95% 355 fewer — 6 fewer)	**Low** Due to very serious imprecision [2]	Helmet NIV may decrease mortality
IMV 9 Critical	Relative risk 0.3 (CI 95% 0.15 — 0.58) Based on data from 83 participants in 1 studies.	**615** per 1000 Difference:	**185** per 1000 **430 fewer per 1000** (CI 95% 523 fewer — 258 fewer)	**Low** Due to very serious imprecision [3]	Helmet NIV may decrease IMV
Hospital LOS	Lower better Based on data from 83 participants in 1 studies. (Randomized controlled)	**7.8** days (Median) Difference:	**4.7** days (Median) **MD 5.1 fewer** (CI 95% 9.38 fewer — 0.82 fewer)	**Low** Due to very serious imprecision [4]	Helmet NIV may decrease hospital LOS
ICU LOS			CI 95%		No studies were found that looked at ICU LOS

1. Mortality at 90d for this outcome. 1 year data not used based on consensus from the SR and WHO groups.
2, 3, 4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Number of patients is far less than would be required to meet the optimal information size (<10%). **Publication bias: no serious.**

3.4.2 Invasive ventilation and management of Acute Respiratory Distress Syndrome (ARDS)

3.4.2.1 Tidal volumes for ventilation

We recommend implementation of mechanical ventilation using lower tidal volumes (4–8 mL/kg predicted body weight [PBW]) and lower inspiratory pressures (plateau pressure < 30 cmH_2O) *[Non-GRADE-based recommendation]*.

Remark for adults:
The implementation of mechanical ventilation using lower tidal volumes and lower inspiratory pressures is a strong recommendation from a clinical guideline for patients with ARDS (70), and is also suggested for patients with sepsis-induced respiratory failure who do not meet ARDS criteria (70). The initial target tidal volume is 6 mL/kg PBW; tidal volume up to 8 mL/kg PBW is allowed if undesirable side-effects occur (e.g. dyssynchrony, pH < 7.15). Permissive hypercapnia is permitted. Ventilator protocols are available (244). The use of deep sedation may be required to control respiratory drive and achieve tidal volume targets.

Remark for children:
In children, a lower level of plateau pressure (< 28 cmH_2O) is targeted, and a lower target of pH is permitted (7.15–7.30). Tidal volumes should be adapted to disease severity: 3–6 mL/kg PBW in the case of poor respiratory system compliance, and 5–8 mL/kg PBW with better preserved compliance (246).

3.4.2.2 Prone ventilation period

In adult patients with severe ARDS (PaO_2/FiO_2 < 150) prone ventilation for 12–16 hours per day is recommended *[Non-GRADE-based recommendation]*.

Remarks:
1. Application of prone ventilation is recommended for adult patients, preferably for 16 hours per day, and may be considered for paediatric patients with severe ARDS but requires sufficient human resources and expertise to be performed safely; protocols (including videos) are available (41)(42).
2. There is little evidence on prone positioning in pregnant women with ARDS; this could be considered in early pregnancy. Pregnant women in the third trimester may benefit from being placed in the lateral decubitus position.

3.4.2.3 Positive end-expiratory pressure (PEEP)

In patients with moderate or severe ARDS, a trial of higher positive end-expiratory pressure (PEEP) instead of lower PEEP is suggested and requires consideration of benefits versus risks. In COVID-19, we suggest the individualization of PEEP where during titration the patient is monitored for effects (beneficial or harmful) and driving pressure *[Non-GRADE-based recommendation].*

Remarks:
1. PEEP titration requires consideration of benefits (reducing atelectrauma and improving alveolar recruitment) vs risks (end-inspiratory overdistension leading to lung injury and higher pulmonary vascular resistance). Tables are available to guide PEEP titration based on the FiO_2 required to maintain SpO_2 (147). In younger children, maximal PEEP pressures are 15 cmH_2O. Although high driving pressure (plateau pressure − PEEP) may more accurately predict increased mortality in ARDS compared with high tidal volume or plateau pressure (148); data from RCTs of ventilation strategies that target driving pressure are not currently available.
2. A related intervention of recruitment manoeuvres (RMs) is delivered as episodic periods of high CPAP (30–40 cmH_2O), progressive incremental increases in PEEP with constant driving pressure, or high driving pressure; considerations of benefits vs risks are similar. Higher PEEP and RMs were both conditionally recommended in a clinical practice guideline. For PEEP, the guideline considered an individual patient data meta-analysis (43) of three RCTs. However, a subsequent RCT of high PEEP and prolonged high-pressure RMs showed harm, suggesting that the protocol in this RCT should be avoided (150). Monitoring of patients to identify those who respond to the initial application of higher PEEP or a different RM protocol and stopping these interventions in non-responders are suggested (44).

3.4.2.4 Neuromuscular blockade

In patients with moderate-severe ARDS (PaO_2/FiO_2 < 150), neuromuscular blockade by continuous infusion should not be routinely used *[Non-GRADE-based recommendation].*

Remark:
A trial found that this strategy improved survival in adult patients with moderate-severe ARDS (PaO_2/FiO_2 < 150) without causing significant weakness (255), but results of a recent larger trial found that use of neuromuscular blockade with high PEEP strategy was not associated with a survival benefit when compared with a light sedation strategy without neuromuscular blockade (256). Intermittent or continuous neuromuscular blockade may still be considered in patients with ARDS, both adults and children, in certain situations: ventilator dyssynchrony despite sedation, such that tidal volume limitation cannot be reliably achieved; or refractory hypoxaemia or hypercapnia.

3.4.2.5 Ventilator connections

Avoid disconnecting the patient from the ventilator, which results in loss of PEEP, atelectasis and increased risk of infection of health care workers *[Non-GRADE-based recommendation].*

Remarks:
1. Use in-line catheters for airway suctioning and clamp endotracheal tube when disconnection is required (for example, transfer to a transport ventilator).
2. Manual hyperinflation should be avoided and ventilator hyperinflation used instead, if indicated (221).

3.4.3 Prevention of complications in critically ill patients with COVID-19

Conditional recommendation for

For patients with COVID-19 who are critically ill, with or without invasive mechanical ventilation, we suggest the use of existing care bundles (defined as three or more evidence informed practices delivered together and consistently to improve care; (see Evidence to decision for examples), chosen locally by the hospital or ICU and adapted as necessary for local circumstances *[Conditional recommendation, very low certainty evidence]*.

Practical info

The GDG made a conditional recommendation in favour of care bundles for critically ill patients with COVID-19. Existing care bundles for critically ill patients include those for reducing delirium and improving cognition and sleep (reviewed in *(85)*; other information available at https://www.icudelirium.org/medical-professionals/overview), preventing VAP *(267)*, treating sepsis (reviewed in http://links.lww.com/CCM/C326), preventing central venous catheter infection *(86)*, and preventing pressure ulcers (https://www.nice.org.uk/guidance/cg179). For some bundles, observational data have shown variable association between the bundle components and patient important outcomes *(268)*. Even in currently accepted care bundles, the components may change as the evidence base evolves. Hospitals and ICUs should choose bundles for which adherence is likely to be high.

Uncertainties
Monitor multiple RCTs in process in patients with COVID-19.

Evidence to decision

Benefits and harms

Some benefits

Indirect evidence in patients without COVID-19 suggest that some care bundles may improve patient-important outcomes, such as mortality, but the effects vary depending on the specific bundle, and the population targeted. The certainty of evidence is generally low to very low. Examples of care bundles in the critically ill can be found in the practical info tab and in the Cochrane Collaboration review of the literature published in the Web Annex. The effect on other outcomes is uncertain.

Potential harms of bundles include the administrative burden of initial implementation, ongoing training, and monitoring of performance (very low certainty).

Certainty of the evidence

Very low

The evidence review consisted of a rapid review by the Cochrane Collaboration, supplemented by references provided by GDG members. The Cochrane review found very low certainty evidence in support of a mortality reduction with implementation of care bundles in critically ill patients. Supplementary references provided low to very low certainty evidence for important effects on mortality with bundles to reduce delirium *(85)*, prevent VAP *(267)*, treat sepsis (http://links.lww.com/CCM/C326), and prevent central venous catheter infection *(86)* and pressure ulcers (https://www.nice.org.uk/guidance/cg179). All evidence reviewed was indirect, from non-COVID-19 populations.

Values and preferences

No substantial variability expected

Applying the agreed values and preferences, the GDG inferred that the majority of well-informed patients would want to receive care bundles, locally adapted as necessary and applicable to their situation, given the low to very low certainty evidence suggesting a reduction in mortality and very low certainty of harm.

Resources and other considerations

Important considerations

Care bundles may contain practices that require adaptation to implement in all settings, depending on their contents. For example, early mobilization and rehabilitation as part of a care bundle to reduce delirium may require additional training, and central line insertion may require multiple sterile towels or a sterile gown placed on the patient, if large sterile drapes are not available.

Justification

When moving from evidence to the conditional recommendation in favour of care bundles for critically ill patients with COVID-19, the panel emphasized the low to very low certainty evidence of reduction in mortality and possible administrative burdens for implementation. The GDG recognized that hospital or ICUs may select among existing care bundles and adapt them to local circumstances as required, based on contextual factors of resource considerations and feasibility. The GDG judged that considerations of accessibility and impact on health equity would not alter the recommendation. The GDG was not aware of ongoing studies of care bundles in the critically ill COVID-19 population.

Subgroup analyses

The panel did not find any evidence bearing on the question of subgroup effects across patients with different levels of disease severity or between children and adults. In other words, the conditional recommendation is applicable across all these subgroups.

Applicability

Special populations

None of the reviewed studies of care bundles enrolled children, and therefore the applicability of this recommendation to children is uncertain. However, the panel thought that the implementation of relevant care bundles for children with COVID-19 would have similar effects to care bundles in adults. Similarly, the panel concluded that the recommendation applies to pregnant women.

Clinical question/ PICO

Population: Patients with COVID-19 and ARDS or viral pneumonia who are critically ill in ICU, with or without invasive ventilation. Populations of children (defined <18 years) and adult patients (≥18 years)

Intervention: Existing validated care bundles*, chosen locally by the hospital or ICU, adapted to local circumstances, and felt to be appropriate for patients with COVID-19 as specified above. *A care bundle is defined as three or more evidence informed practices delivered together and consistently to improve care.

Comparator: Not using existing care bundles

Outcome Timeframe	**Study results and measurements**	**Comparator** No care bundles	**Intervention** Care bundles	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality (randomized trials) at 6 months	Relative risk 0.75 (CI 95% 0.53 — 1.06) Based on data from 180 participants in 1 studies. (Randomized controlled)	**489** per 1000 Difference:	**367** per 1000 **122 fewer per 1000** (CI 95% 259 fewer — 29 more)	**Very low** Due to very serious indirectness, Due to very serious imprecision [1]	ICU care bundles possibly reduce mortality
Mortality (observational studies) 28 days or to hospital discharge	Relative risk 0.75 (CI 95% 0.65 — 0.86) Based on data from 1,258 participants in 7 studies. (Observational (non-randomized))	**359** per 1000 Difference:	**269** per 1000 **90 fewer per 1000** (CI 95% 126 fewer — 50 fewer)	**Very low** Due to very serious indirectness, Due to very serious imprecision [2]	ICU care bundles possibly reduce mortality
Administrative burden	Based on data from 0 participants in 0 studies.			**Very low**	Care bundles may be associated with an appreciable administrative burden.

Outcome Timeframe	**Study results and measurements**	**Comparator** No care bundles	**Intervention** Care bundles	**Certainty of the evidence** (Quality of evidence)	**Summary**
Impingement on physician autonomy	Based on data from 0 participants in 0 studies.			**Very low**	Care bundles may be associated with an impingement of physician autonomy.

1, 2. **Inconsistency: no serious. Indirectness: very serious. Imprecision: very serious. Publication bias: no serious.**

Info Box

Table 13.1 shows interventions to prevent complications in hospitalized and critically ill patients with COVID-19. They are based on Surviving Sepsis *(70)* or other guidelines *(267)(272)(87)(88)*, and are generally limited to feasible recommendations based on high-quality evidence. Recent publications have encouraged best practices to continue during the COVID-19 outbreak *(273)*. See the WHO *Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation* for practical tools to assist implementation *(161)*.

Table 13.1 Interventions to prevent complications in hospitalized and critically ill patients with COVID-19

Anticipated outcome	Interventions
Reduce days of invasive mechanical ventilation	• Use weaning protocols that include daily assessment for readiness to breathe spontaneously • Minimize continuous or intermittent sedation, targeting specific titration endpoints (light sedation unless contraindicated) or with daily interruption of continuous sedative infusions • Early mobilization • Implementation of the above as a bundle of care (may also reduce delirium); such as the **A**wakening and **B**reathing **C**oordination, **D**elirium assessment/management, and **E**arly mobility (ABCDE)
Reduce incidence of ventilator-associated pneumonia	• Oral intubation is preferable to nasal intubation in adolescents and adults • Keep patient in semi-recumbent position (head of bed elevation 30–45º) • Use a closed suctioning system; periodically drain and discard condensate in tubing • Use a new ventilator circuit for each patient; once patient is ventilated, change circuit if it is soiled or damaged, but not routinely • Change heat moisture exchanger when it malfunctions, when soiled, or every 5–7 days
Reduce incidence of catheter-related bloodstream infection	• Use a checklist with completion verified by a real-time observer as a reminder of each step needed for sterile insertion and as a daily reminder to remove catheter if no longer needed
Reduce incidence of pressure ulcers	• Turn patient every 2 hours
Reduce incidence of stress ulcers and GI bleeding	• Give early enteral nutrition (within 24–48 hours of admission) • Administer histamine-2 receptor blockers or proton-pump inhibitors in patients with risk factors for GI bleeding. Risk factors for GI bleeding include mechanical ventilation for ≥ 48 hours, coagulopathy, renal replacement therapy, liver disease, multiple comorbidities, and higher organ failure score
Reduce the development of antimicrobial resistance	• Utilize de-escalation protocols as soon as patient is clinically stable and there is no evidence of bacterial infection
Reduce the development of adverse drug effects	• Expose patient to empiric antimicrobial therapy for the shortest time possible, to prevent nephrotoxicity, cardiac and other side-effects from unnecessary antimicrobial use
Promote appropriate antimicrobial prescribing and use during the COVID-19 pandemic *(274)*	• Do not prescribe antibiotics to suspected or confirmed COVID-19 patients with low suspicion of a bacterial infection, to avoid more short-term side-effects of antibiotics in patients and negative long-term consequences of increased antimicrobial resistance

3.5 Multi-system inflammatory syndrome in children (MIS-C) with COVID-19

This section outlines what information the GDG requested and used in making their recommendations for corticosteroids in hospitalized children with COVID-19 aged 0 to 18 years, who meet standardized clinical definition for MIS-C (see Annex 5 for standardized definitions).

Prioritized outcomes

For the previous recommendations, the GDG members prioritized outcomes (rating from 9 [critical] to 1 [not important]) with severe and critical COVID-19, taking a patient perspective (Table 2.1). For these new recommendations on MIS-C, the GDG concluded that the values and preferences of children and adolescents with MIS-C may differ from those used in previous recommendations. A new targeted outcomes prioritization exercise was conducted (Table 14.1). These new prioritized outcomes were used to update the meta-analysis.

Values and preferences

For these new recommendations for MIS-C, the majority of GDG members inferred that most well-informed patients, and their families, would, despite the high uncertainty of important benefit, want to receive some therapeutic agent in addition to supportive care for MIS-C, compared with no specific therapeutic agent. In doing so, patients would be placing a high value on uncertain benefit and a low value on avoiding any mild adverse effects associated with treatment.

Table 14.1. Panel outcome rating from a patient perspective and a parent perspective of MIS-C

Outcome	Median	Mean	SD	Range
Death	9	8.81	0.56	7-9
Need for invasive mechanical ventilation	8	8.07	0.94	6-9
Need for haemodynamic support	8	7.48	1.52	3-9
Severe adverse effects	7	7.23	0.93	5-9
Quality of life	7	7.19	1.28	3-9
Cardiac aneurysms at discharge	7	6.96	1.57	2-9
Change in cardiac function compared to baseline	7	6.74	1.38	3-9
Persistent symptoms at 3 months	6	6.37	1.57	3-9
Duration of hospitalization	6	6.04	1.62	2-9
Length of stay in PICU	6	6	1.36	4-8
Time to symptom resolution	6	5.74	1.55	2-8
Fever present more than 48 hours after treatment	5	4.81	1.85	1-7

PICU: Paediatric intensive care unit; SD: standard deviation.
Note: 7 to 9 – critical; 4 to 6 – important; 1 to 3 – of limited importance.

Evidence summary

The GDG's recommendations for corticosteroid use in hospitalized children who meet the standard clinical definition for MIS-C were informed by the results of systematic review and meta-analysis of the literature that pooled data from 3 studies, n = 885 *(89)(90)(275)*. In Annexes 3 and 4, the systematic search criteria and table of trial characteristics can be found, respectively.

From these studies, for the three comparisons: a) adding corticosteroids to IVIG compared to IVIG alone; b) corticosteroids compared to IVIG; and c) adding corticosteroids to IVIG compared to corticosteroids alone and for all prioritized outcomes including death, need for invasive mechanical ventilation two days after initiation of treatment, need for hemodynamic support two days after initiation of treatment, coronary artery dilation, acute left ventricular dysfunction 2 days after initiation of treatment, and reduction in fever 2 days after initiation of treatment, the evidence was of very low certainty.

The evidence was summarized in the summary of findings tables and presented to the GDG addressing the pre-specified PICOs and prioritized outcomes: corticosteroids + IVIG vs IVIG alone; corticosteroids alone vs IVIG alone; and corticosteroids + IVIG vs corticosteroids alone (see Research Evidence tab) below). For all three PICOs, very low certainty evidence was ascertained for all outcomes.

Subgroup analysis

Subgroup analyses were not conducted.

Conditional recommendation for

- **In hospitalized children aged 0–18 who meet a standard case definition for MIS-C, we suggest using corticosteroids in addition to supportive care (rather than either IVIG plus supportive care, or supportive care alone)** *[Conditional recommendation, very low certainty evidence].*
- **In hospitalized children aged 0–18 who meet both a standard case definition for MIS-C and diagnostic criteria for Kawasaki disease, we suggest using corticosteroids in addition to standard of care for Kawasaki disease** *[Conditional recommendation, very low certainty evidence].*

Practical info

Practical info

There are slightly different case definitions for MIS-C (Annex 5). This guideline is applicable for any standard case definition of MIS-C. Case definitions will continue to be updated as new data emerge. Based on accessibility to corticosteroids being much wider than accessibility to IVIG, the panel suggested that most patients will receive corticosteroids before they receive IVIG, even in patients where both are prescribed.

Route: Systemic corticosteroids can be given orally or intravenously. All studies examined intravenous administration.

Dose and duration: In the three studies included in the meta-analysis, intravenous methylprednisilone was used at varying doses; one study did not report a dose. The other two reported ranges between 0.8–2.0 mg/kg/day for 5 days; or higher bolus doses of 10–30 mg/kg/day for 3 days. Both lower and higher dose options can be considered. See Annex 4 for study details.

Monitoring: It would be prudent to monitor for known complications associated with corticosteroid use, such as hyperglycemia and behavioural changes.

Supportive care: Most emphatically, the GDG emphasized the importance of high-quality supportive care to improve the outcomes of these children, apart from specific therapies. Please see the *WHO Pocket Book of Hospital Care for Children* for syndromic management guidance of severely ill children, including the importance of recognizing other conditions such leading to shock, sepsis and severe infections; as well as guidance from other organizations on supportive management of Kawasaki disease *(83)*.

Uncertainties

The GDG emphasized the need for further randomized clinical trials in this population with these agents. The panel acknowledged that results of ongoing randomized trials of therapeutic interventions for MIS-C over the next several months were highly likely to upgrade the certainty of evidence and may lead to changes in recommendations. Enrolment of patients into randomized trials should be prioritized.

Evidence to decision

Benefits and harms

Supportive care/standard of care: The GDG emphasized the importance of optimized supportive care for children meeting the standardized case definition of MIS-C. Thus, the interpretation of these results, should consider that supportive care is the current standard of care on which these interventions are additive. See *WHO Pocket Book of Hospital Care for Children (83)*, and the *WHO Paediatric emergency triage, assessment and treatment: care of critically ill children (219)*.

Interventions:

- The effects of corticosteroids in addition to IVIG, compared with IVIG alone plus supportive care, or supportive care alone, all prioritized outcomes, including death during hospitalization, need for mechanical ventilation, coronary artery abnormalities, and cardiac dysfunction are very uncertain (very low certainty, direct evidence).
- The effects of corticosteroids alone, compared with IVIG plus supportive care, or supportive care alone on all prioritized outcomes, including death during hospitalization, need for mechanical ventilation, coronary artery abnormalities, and cardiac dysfunction are very uncertain (very low certainty, direct evidence).

- The effects of corticosteroids in addition to IVIG compared to corticosteroids alone on all prioritized outcomes including death during hospitalization, need for mechanical ventilation, and other prioritized outcomes are very uncertain (very low certainty, direct evidence).

Based on the clinical experience of the GDG of other conditions, the possible harms of steroids were deemed to be of lesser importance than the possible benefits. However, the GDG did emphasize that for appropriate evaluation and management for undifferentiated children presenting with shock, consider other serious infections based on epidemiologic considerations (i.e., malaria, HIV, etc). Possible harms of IVIG, based on the clinical experience of the panel of other conditions, include fluid overload due to the volume of IVIG preparations. The GDG acknowledged the care of Kawasaki disease, a clinically similar condition which can be difficult to distinguish from MIS-C, includes IVIG *(83)*.

Certainty of the evidence

Very low

For all outcomes in the three pre-specified PICOs, the GDG considered the evidence to be of very low certainty, due to risk of bias from observational designs and due to serious imprecision (confidence intervals included both important benefit and important harm). The evidence for corticosteroids and IVIG is from observational studies that compare the combination of these agents against them individually.

Values and preferences

Variability expected

The majority of GDG members inferred that most well-informed patients, and their families, would, despite the high uncertainty of important benefit, want to receive some therapeutic agent in addition to supportive care for MIS-C, compared with no specific therapeutic agent. In doing so, patients would be placing a high value on uncertain benefit and a low value on avoiding any mild adverse effects associated with treatment.

Resources and other considerations

Important considerations

Corticosteroids are widely available in all regions of the world and methylprednisolone is on the WHO Model List of Essential Medicines. IVIG has important resource considerations, including higher cost, and is not readily available across all care settings and regions.

Justification

When moving from evidence to the conditional recommendations for children hospitalized with MIS-C, the panel emphasized the very low certainty evidence of reduction in mortality and the need for haemodynamic support and mechanical ventilation with the use of corticosteroids. The panel also acknowledged that some children will simultaneously meet diagnostic criteria for Kawasaki disease, and the standard of care in many parts of the world is to use IVIG, where available, in that population. The panel emphasized the practical difficulty in differentiating the two populations, leading to the emphasis on IVIG in care pathways, despite the lack of supporting direct evidence. In the absence of randomized evidence showing IVIG to be harmful, the panel expressed concern about not providing IVIG, where available, to children who meet diagnostic criteria of both Kawasaki disease and MIS-C. The panel acknowledged that ongoing randomized trials are expected to add substantially to the evidence base over the next several months.

Subgroup analyses

Given the available evidence, the panel did not find any evidence bearing on the question of subgroup effects across patients with different levels of disease severity, and therefore did not make any subgroup recommendations. In other words, the conditional recommendations are applicable across all patient subgroups. In particular, there are insufficient data to support different recommendations in the younger age ranges (given the predilection for younger age ranges in Kawasaki disease). Analyses based on dose of corticosteroid or IVIG administered were unable to be performed, given the limitations of the studies.

Applicability

Special populations

There was no special population where the panel inferred different applicability of these recommendations.

Clinical question/ PICO

Population: Children aged 0–19 years meeting any standard case definition of MIS-C in hospitals in high-income countries (HIC) and low- and middle-income countries (LMIC)

Intervention: IVIG plus steroids as the initial treatment

Comparator: IVIG alone as the initial treatment

Outcome Timeframe	**Study results and measurements**	**Comparator** IVIG alone as the initial treatment	**Intervention** IVIG plus steroids as the initial treatment	**Certainty of the evidence** (Quality of evidence)	**Summary**
Death during hospitalization	Odds ratio 0.32 (CI 95% 0.05 — 1.86) Based on data from 334 participants in 1 studies. [1] (Observational (non-randomized))	**16** per 1000 Difference:	**5** per 1000 **11 fewer per 1000** (CI 95% 15 fewer — 14 more)	**Very low** Due to very serious risk of bias and serious imprecision [2]	The evidence is very uncertain about the effect of adding steroids to IVIG on death during hospitalization
Ventilation support 2 days after initiation of treatment	Odds ratio 0.52 (CI 95% 0.1 — 2.76) Based on data from 429 participants in 2 studies. [3] (Observational (non-randomized))	**210** per 1000 Difference:	**109** per 1000 **101 fewer per 1000** (CI 95% 189 fewer — 370 more)	**Very low** Due to very serious risk of bias, serious inconsistency, and serious imprecision [4]	The evidence is very uncertain about the effect of adding steroids to IVIG on the need for ventilation support 2 days after initiation of treatment
Haemodynamic support 2 days after initiation of treatment	Odds ratio 0.52 (CI 95% 0.32 — 0.83) Based on data from 551 participants in 3 studies. [5] (Observational (non-randomized))	**580** per 1000 Difference:	**302** per 1000 **278 fewer per 1000** (CI 95% 395 fewer — 99 fewer)	**Very low** Due to very serious risk of bias [6]	The evidence is very uncertain about the effect of adding steroids to IVIG results in a reduction in the need for haemodynamic support 2 days after initiation of treatment
Coronary artery dilatation at discharge	Odds ratio 0.46 (CI 95% 0.05 — 4.22) Based on data from 224 participants in 1 studies. [7] (Observational (non-randomized))	**5** per 1000 Difference:	**2** per 1000 **3 fewer per 1000** (CI 95% 5 fewer — 16 more)	**Very low** Due to very serious risk of bias and serious imprecision [8]	The evidence is very uncertain about the effect of adding steroids to IVIG on coronary artery dilatation at discharge
Acute left ventricular dysfunction 2 days after initiation of treatment	Odds ratio 0.55 (CI 95% 0.18 — 1.67) Based on data from 543 participants in 3 studies. [9] (Observational (non-randomized))	**520** per 1000 Difference:	**373** per 1000 **147 fewer per 1000** (CI 95% 357 fewer — 124 more)	**Very low** Due to very serious risk of bias and serious imprecision [10]	The evidence is very uncertain about the effect of adding steroids to IVIG on acute left ventricular dysfunction 2 days after initiation of treatment
Clinical improvement 2 days after initiation of treatment	Odds ratio 1.09 (CI 95% 0.53 — 2.23) Based on data from 304 participants in 1 studies. [11] (Observational (non-randomized))	**268** per 1000 Difference:	**292** per 1000 **24 more per 1000** (CI 95% 126 fewer — 329 more)	**Very low** Due to very serious risk of bias and serious imprecision [12]	The evidence is very uncertain about the effect of adding steroids to IVIG on clinical improvement 2 days after initiation of treatment

Outcome Timeframe	Study results and measurements	Comparator IVIG alone as the initial treatment	Intervention IVIG plus steroids as the initial treatment	Certainty of the evidence (Quality of evidence)	Summary
Fever persisting 2 days after initiation of treatment	Odds ratio 0.69 (CI 95% 0.5 — 0.95) Based on data from 661 participants in 3 studies. [13] (Observational (non-randomized))	**993** per 1000 Difference:	**685** per 1000 **307 fewer per 1000** (CI 95% 497 fewer — 50 fewer)	**Very low** Due to very serious risk of bias [14]	The evidence is very uncertain about the effect of adding steroids to IVIG results in a reduction in fever 2 days after initiation of treatment

1, 7, 11. with included studies: [89].
2, 8, 10, 12. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect.. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect..
3. with included studies: [89], [90].
4. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect.. **Inconsistency: serious.** Downgraded for inconsistency as I squared > 50% or p value represented presence of statistical heterogeneity. Random effects model for pooling ORs was used. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect..
5, 13. with included studies: [90], [89], [275].
6, 14. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect..
9. with included studies: [89], [275], [90].

Clinical question/ PICO

Population: Children aged 0–19 years meeting any standard case definition of MIS-C in hospitals in high-income countries (HIC) and low- and middle-income countries (LMIC)

Intervention: IVIG plus steroids as the initial treatment

Comparator: Steroids alone as the initial treatment

Outcome Timeframe	Study results and measurements	Comparator Steroids alone as the initial treatment	Intervention IVIG plus steroids as the initial treatment	Certainty of the evidence (Quality of evidence)	Summary
Death during hospitalization	Based on data from 233 participants in 1 studies. [1] (Observational (non-randomized))	**0** per 1000	**24** per 1000	**Very low** Due to very serious risk of bias and serious imprecision [2]	The evidence is very uncertain about the effect of adding IVIG to steroids on death during hospitalization
Ventilation support 2 days after initiation of treatment	Odds ratio 3.7 (CI 95% 0.88 — 16.67) Based on data from 234 participants in 1 studies. [3] (Observational (non-randomized))	**62** per 1000 Difference:	**230** per 1000 **168 more per 1000** (CI 95% 7 fewer — 971 more)	**Very low** Due to very serious risk of bias and serious imprecision [4]	The evidence is very uncertain about the effect of adding IVIG to steroids on the need for ventilation support 2 days after initiation of treatment
Haemodynamic support 2 days after initiation of	Odds ratio 1.75 (CI 95% 0.64 — 4.76) Based on data from 238	**164** per 1000	**288** per 1000	**Very low** Due to very serious risk of bias and	The evidence is very uncertain about the effect of adding IVIG to steroids

Outcome Timeframe	Study results and measurements	Comparator Steroids alone as the initial treatment	Intervention IVIG plus steroids as the initial treatment	Certainty of the evidence (Quality of evidence)	Summary
treatment	participants in 1 studies. [5] (Observational (non-randomized))	Difference:	**123 more per 1000** (CI 95% 59 fewer — 617 more)	serious imprecision [6]	on the need for haemodynamic support 2 days after initiation of treatment
Coronary artery dilatation at discharge	Odds ratio 0.61 (CI 95% 0.06 — 5.88) Based on data from 159 participants in 1 studies. [7] (Observational (non-randomized))	**4** per 1000 Difference:	**3** per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 21 more)	**Very low** Due to very serious risk of bias and serious imprecision [8]	The evidence is very uncertain about the effect of adding IVIG to steroids on coronary artery dilatation at discharge
Acute left ventricular dysfunction 2 days after initiation of treatment	Odds ratio 2.08 (CI 95% 0.56 — 7.69) Based on data from 238 participants in 1 studies. [9] (Observational (non-randomized))	**81** per 1000 Difference:	**169** per 1000 **88 more per 1000** (CI 95% 36 fewer — 542 more)	**Very low** Due to very serious risk of bias and serious imprecision [10]	The evidence is very uncertain about the effect of adding IVIG to steroids on acute left ventricular dysfunction 2 days after initiation of treatment
Clinical improvement 2 days after initiation of treatment	Odds ratio 0.56 (CI 95% 0.24 — 1.32) Based on data from 212 participants in 1 studies. [11] (Observational (non-randomized))	**408** per 1000 Difference:	**228** per 1000 **180 fewer per 1000** (CI 95% 310 fewer — 129 more)	**Very low** Due to very serious risk of bias and serious imprecision [12]	The evidence is very uncertain about the effect of adding IVIG to steroids on clinical improvement 2 days after initiation of treatment
Fever persisting 2 days after initiation of treatment	Odds ratio 1.3 (CI 95% 0.55 — 3.23) Based on data from 195 participants in 1 studies. [13] (Observational (non-randomized))	**356** per 1000 Difference:	**475** per 1000 **119 more per 1000** (CI 95% 160 fewer — 792 more)	**Very low** Due to very serious risk of bias and serious imprecision [14]	The evidence is very uncertain about the effect of adding IVIG to steroids on fever persisting two days after initiation of treatment

1. with included studies: [89]. Adjusted relative risk not available..
2, 4, 6, 8, 10, 12, 14. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect.. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect..
3, 5, 7, 9, 11, 13. with included studies: [89].

Clinical question/ PICO

Population: Children aged 0–19 years meeting any standard case definition of MIS-C in hospitals in high-income countries (HIC) and low- and middle-income countries (LMIC)

Intervention: Steroids alone as the initial treatment

Comparator: IVIG alone as the initial treatment

Outcome Timeframe	**Study results and measurements**	**Comparator** IVIG alone as the initial treatment	**Intervention** Steroids alone as the initial treatment	**Certainty of the evidence** (Quality of evidence)	**Summary**
Death during hospitalization	Based on data from 239 participants in 1 studies. [1] (Observational (non-randomized))	**16** per 1000	**0** per 1000	**Very low** Due to very serious risk of bias and serious imprecision [2]	The evidence is very uncertain about the effect of steroids alone compared with IVIG alone on death during hospitalization
Ventilation support 2 days after initiation of treatment	Odds ratio 0.31 (CI 95% 0.07 — 1.43) Based on data from 237 participants in 1 studies. [3] (Observational (non-randomized))	**93** per 1000 Difference:	**29** per 1000 **64 fewer per 1000** (CI 95% 86 fewer — 40 more)	**Very low** Due to very serious risk of bias and serious imprecision [4]	The evidence is very uncertain about the effect of steroids alone compared with IVIG alone on the need for ventilation support 2 days after initiation of treatment
Haemodynamic support 2 days after initiation of treatment	Odds ratio 0.43 (CI 95% 0.15 — 1.22) Based on data from 241 participants in 1 studies. [5] (Observational (non-randomized))	**276** per 1000 Difference:	**119** per 1000 **157 fewer per 1000** (CI 95% 234 fewer — 61 more)	**Very low** Due to very serious risk of bias and serious imprecision [6]	The evidence is very uncertain about the effect of steroids alone compared with IVIG alone on the need for haemodynamic support 2 days after initiation of treatment
Coronary artery dilatation at discharge	Odds ratio 0.75 (CI 95% 0.18 — 3.22) Based on data from 171 participants in 1 studies. [7] (Observational (non-randomized))	**5** per 1000 Difference:	**4** per 1000 **1 fewer per 1000** (CI 95% 4 fewer — 11 more)	**Very low** Due to very serious risk of bias and serious imprecision [8]	The evidence is very uncertain about the effect of steroids alone compared with IVIG alone on coronary artery dilatation at discharge
Acute left ventricular dysfunction 2 days after initiation of treatment	Odds ratio 0.69 (CI 95% 0.18 — 2.62) Based on data from 243 participants in 1 studies. [9] (Observational (non-randomized))	**110** per 1000 Difference:	**76** per 1000 **34 fewer per 1000** (CI 95% 90 fewer — 178 more)	**Very low** Due to very serious risk of bias and serious imprecision [10]	The evidence is very uncertain about the effect of steroids alone compared with IVIG alone on acute left ventricular dysfunction 2 days after initiation of treatment
Clinical improvement 2 days after initiation of treatment	Odds ratio 1.95 (CI 95% 0.83 — 4.6) Based on data from 212 participants in 1 studies. [11] (Observational (non-randomized))	**268** per 1000 Difference:	**522** per 1000 **254 more per 1000** (CI 95% 45 fewer — 965 more)	**Very low** Due to very serious risk of bias and serious imprecision [12]	The evidence is very uncertain about the effect of steroids alone compared with IVIG alone on clinical improvement 2 days after initiation of treatment
Fever persisting 2 days after initiation of treatment	Odds ratio 0.51 (CI 95% 0.21 — 1.2) Based on data from 208 participants in 1 studies. [13] (Observational (non-randomized))	**473** per 1000 Difference:	**241** per 1000 **232 fewer per 1000** (CI 95% 374 fewer — 95 more)	**Very low** Due to very serious risk of bias and serious imprecision [14]	The evidence is very uncertain about the effect of steroids alone compared with IVIG alone on fever persisting 2 days after initiation of treatment

1. with included studies: [89]. Adjusted relative risk not available..
2, 4, 6, 8, 10, 12, 14. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect.. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect..
3, 5, 7, 9, 11, 13. with included studies: [89].

3.6 Treatment of other acute and chronic infections in patients with COVID-19

The prevalence of acute coinfections or secondary infections coinciding with COVID-19 has been imprecisely described but appears to be low *(198)*, and will be based on local factors and endemic or other emerging infections *(65)(210)(212)(274)*. Antibiotic overuse increases the risk of emergence and transmission of multidrug-resistant bacteria. Infections with multidrug-resistant bacteria are more difficult to treat, and associated with increased morbidity and mortality.

For general advice in navigating the challenges of reducing unnecessary antibiotic use, please see *Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries: a WHO practical toolkit (583)*.

3.6.1 Use of antibiotics in non-severe COVID-19

New

Strong recommendation against

For patients with *non-severe COVID-19* and a low clinical suspicion of a concurrent bacterial infection, we recommend no antibiotics *[Strong recommendation, low/moderate certainty evidence]*.

Remarks:

1. *Clinical suspicion is based on elements of history, physical examination, and laboratory assessment.*
2. *The degree of suspicion of concurrent bacterial infection, even if low at hospital admission, may increase over time as the patient's clinical status evolves.*
3. *The recommendation does not apply to situations where the clinical suspicion of a concurrent bacterial infection is not low, for example a probability of infection >10%.*

Practical info

At present, robust scoring systems which evaluate the probability of bacterial infection in COVID-19 do not exist. The recommendation suggests that “low risk” is less than 10% probability, and must therefore be based on all the complex information available to the clinician ("gestalt"). This will be reviewed as any new objective measures are validated.

Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

Overall, there are probably no beneficial effect of empirical antibiotics for patients with non-severe COVID-19. Specifically, there may be little to no effect of antibiotics on mortality in high-risk and moderate-risk patients (low-certainty evidence) and there is probably little to no effect of antibiotics on mortality in low-risk patients (moderate-certainty evidence). There is probably little to no effect of antibiotics on hospital admission (moderate-certainty evidence). High-certainty evidence suggests little to no effect of antibiotics on the need for mechanical ventilation and on serious adverse events.

Studies did not report effects of empirical antibiotics on antimicrobial resistance.

Certainty of the evidence

Low

As noted above, certainty of evidence was low for mortality in high-risk and moderate-risk patients; moderate for mortality in low-risk patients and hospital admission; and high for need for mechanical ventilation and serious adverse events.

Values and preferences

No substantial variability expected

The panel believed that considerations of the risk of antimicrobial resistance in the population are also important, in addition to individual patient considerations, which include severity of disease.

In patients with non-severe COVID-19 and low clinical suspicion of a concurrent bacterial infection, the risk of antimicrobial resistance was felt to be the dominant consideration, given the probable lack of benefit of empirical antibiotics.

Resources and other considerations

No important issues with the recommended alternative

Antibiotics are generally available, although the availability of specific antibiotics may depend on the particular setting. Avoidance of antibiotics that are of no probable benefit would be expected to reduce costs for patients.

Justification

The panel reviewed new meta-analysis of the outcomes of patients in COVID-19.*(584)*

In making a strong recommendation against antibiotics for patients with non-severe COVID-19 and a low clinical suspicion of a concurrent bacterial infection, the panel judged the risk of antimicrobial resistance as important and noted the overall low or moderate certainty evidence of no effect on mortality and other outcomes.

The panel also noted that clinical suspicion of infection is not a static judgement but could change during the patient's hospital course, and this recommendation only applies when the clinical suspicion of a concurrent bacterial infection is low (≤10%). A systematic review and meta-analysis of bacterial co-infection in patients presenting with COVID-19 to hospital found that 4.9% (95%CI 3.2%-7.6%; n=28 724) of patients had bacterial co-infection identified within 48 hours of hospital admission and 8.4% (95% CI 6.0%-11.7%; n=6638) had co-infection within 48 hours of ICU admission *(216)*. Another systematic review identified ICU admission and mechanical ventilation as the only significant risk factors for bacterial co-infection *(580)*.

Knowledge gaps include how patients at low-risk of bacterial infection can be identified in a structured and objective manner. Quantifying the effect of unnecessary antimicrobial use on broader patterns of antimicrobial resistance is also a priority.

Clinical question/ PICO

Population: People with confirmed SARS-CoV-2 infection with non-severe disease
Intervention: Empiric antibiotics + standard of care
Comparator: Standard of care

Summary

Estimated rates of mortality have been taken from WHO Therapeutics and COVID-19: living guideline. These are 60/1000, 30/1000 and 5/1000 for those at high, moderate and low risk of mortality respectively. Other endpoints have taken estimates from the “standard of care” arms of the included clinical trials. For mortality outcomes, we used the risk difference calculated in the meta-analysis to calculate estimates of absolute effects and confidence intervals in the intervention group. For other outcomes, the relative risk was used.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard of care	**Intervention** Antibiotics	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality (high risk) [1]	Relative risk 1.06 (CI 95% 0.22 — 5.22) Based on data from 1,225 participants in 4 studies. [2] (Randomized controlled)	**60** per 1000 Difference:	**60** per 1000 **0 fewer per 1000** 27 fewer — 27 more	**Low** Due to very serious imprecision [3]	There may be little to no effect of antibiotics on mortality in high risk patients
Mortality (moderate risk) [4]	Relative risk 1.06 (CI 95% 0.22 — 5.22) Based on data from 1,225 participants in 4 studies. [5] (Randomized controlled)	**30** per 1000 Difference:	**30** per 1000 **0 fewer per 1000** 19 fewer — 19 more	**Low** Due to very serious imprecision [6]	There may be little to no effect of antibiotics on mortality in moderate risk patients
Mortality (low risk) [7]	Relative risk 1.06 (CI 95% 0.22 — 5.22) Based on data from 1,225 participants in 4 studies. [8] (Randomized controlled)	**5** per 1000 Difference:	**5** per 1000 **0 fewer per 1000** 8 fewer — 8 more	**Moderate** Due to serious imprecision [9]	There is probably little to no effect of antibiotics on mortality in low risk patients
Hospital admission	Relative risk 0.94 (CI 95% 0.61 — 1.46) Based on data from 1,952 participants in 5 studies. [10]	**40** per 1000 Difference:	**38** per 1000 **2 fewer per 1000** (CI 95% 16 fewer — 18 more)	**Moderate** Due to serious imprecision [11]	There is probably little to no effect of antibiotics on hospital admission
Mechanical ventilation	Relative risk 0.58 (CI 95% 0.19 — 1.77) Based on data from 1,135 participants in 2 studies.	**15** per 1000 Difference:	**9** per 1000 **6 fewer per 1000** (CI 95% 12 fewer — 12 more)	**High**	There is little to no effect of antibiotics on mechanical ventilation
Serious adverse events	Relative risk 1 (CI 95% 0.1 — 9.54) Based on data from 823 participants in 3 studies. (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 9 fewer — 9 more)	**High**	There is little to no effect of antibiotics on serious adverse events

2, 5, 8, 10. **Supporting references:** [120],
3, 6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals. **Publication bias: no serious.**
9. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**
11. **Imprecision: serious.** Wide confidence intervals.

3.6.2 Use of antibiotics in severe COVID-19

New

Conditional recommendation against

For patients with *severe COVID-19* and a low clinical suspicion of a concurrent bacterial infection, we suggest no antibiotics *[Conditional recommendation, low certainty evidence]*.

Remarks:

1. *Clinical suspicion is based on elements of history, physical examination, and laboratory assessment.*
2. *The degree of suspicion of concurrent bacterial infection, even if low at hospital admission, may increase over time as the patient's clinical status evolves.*
3. *The recommendation does not apply to situations where the clinical suspicion of a concurrent bacterial infection is not low, for example a probability of infection >10%.*

Practical info

At present, robust scoring systems which evaluate the probability of bacterial infection in COVID-19 do not exist. The recommendation suggests that “low risk” is less than 10% probability, and must therefore be based on all the complex information available to the clinician ("gestalt"). This will be reviewed as any new objective measures are validated.

Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

Antibiotics may reduce mortality in patients with severe COVID-19 and a low clinical suspicion of a concurrent bacterial infection (low-certainty evidence). Antibiotics probably have little to no effect on mechanical ventilation (moderate-certainty evidence) and little to no effect on serious adverse events (high-certainty evidence).

Certainty of the evidence

Low

Evidence was low-certainty for mortality, moderate-certainty for mechanical ventilation, and high-certainty for serious adverse events.

Values and preferences

Substantial variability is expected or uncertain

The panel believed that considerations of the risk of antimicrobial resistance in the population are also important, in addition to individual patient considerations, which include severity of disease.

In patients with severe COVID-19 and low clinical suspicion of a concurrent bacterial infection, the panel felt that most patients, but not all, would decline antibiotics; some might accept them in view of low-certainty evidence for a reduced risk of mortality.

Resources and other considerations

No important issues with the recommended alternative

Antibiotics are generally available, although the availability of specific antibiotics may depend on the particular setting. Avoidance of antibiotics for most patients with severe COVID-19 and a low clinical suspicion of a concurrent bacterial infection would be expected to reduce health system costs and health care worker workload.

Justification

In making a conditional recommendation against antibiotics for patients with severe COVID-19 and a low clinical suspicion of a concurrent bacterial infection, the panel judged that most patients would decline antibiotics in view of low-certainty evidence of a small (<1%) reduction in mortality. However, some may accept antibiotics in those circumstances; the evidence for a mortality benefit was considered low certainty (estimated 6 in 1000 with 95%CI which spanned significant benefit of 21/1000 fewer deaths to significant harm of 13/1000 more). Any benefit would be expected to be minimal when applied to patients in which bacterial infection was low (≤10%). The panel also took seriously the important risk of development of antimicrobial resistance in the population due to inappropriate administration.

Bacterial infection within 48 hours of admission: A systematic review and meta-analysis of bacterial co-infection in patients presenting with COVID-19 to hospital found that 4.9% (95%CI 3.2%-7.6%; n=28 724) of patients had co-infection identified within 48 hours of hospital admission and 8.4% (95% CI 6.0%-11.7%; n=6638) had co-infection within 48 hours of ICU admission *(216)*. Another systematic review identified ICU admission and mechanical ventilation as the only significant risk factors for bacterial co-infection *(580)*.

Bacterial infection 48 hours and more after admission: A systematic review found that 8.4% (95% CI 6.7%-10.3%) of hospitalised patients and 39.9% (31.1%-49.5%) of ICU patients developed a secondary bacterial infection (arising >48 hours after admission) *(216)*.

The panel also noted that clinical suspicion of infection is not a static judgement but could change during the patient's hospital or ICU course, and should be frequently re-evaluated. As noted, this recommendation only applies when the clinical suspicion of a concurrent bacterial infection is low (≤10% probability).

Clinical question/ PICO

Population: People with confirmed SARS-CoV-2 infection with severe disease
Intervention: Empiric antibiotics + standard of care
Comparator: Standard of care

Summary

Baseline estimates of absolute risk taken from the control arms of the available RCTs. For mortality, mechanical ventilation and serious adverse events (SAE), the absolute effects for the intervention group were calculated using the relative risk estimate from meta-analysis.

Outcome Timeframe	**Study results and measurements**	**Comparator** No antibiotics	**Intervention** Antibiotics	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality [1]	Relative risk 0.97 (CI 95% 0.9 — 1.06) Based on data from 9,243 participants in 6 studies.	**213** per 1000 Difference:	**207** per 1000 **6 fewer per 1000** (CI 95% 21 fewer — 13 more)	**Low** Due to very serious imprecision [2]	Antibiotics may reduce mortality
Mechanical ventilation	Relative risk 0.93 (CI 95% 0.8 — 1.07) Based on data from 8,011 participants in 4 studies. (Randomized controlled)	**95** per 1000 Difference:	**88** per 1000 **7 fewer per 1000** (CI 95% 19 fewer — 7 more)	**Moderate** Due to serious imprecision [3]	There is probably little to no effect of antibiotics on mechanical ventilation.
Serious adverse events	Relative risk 0.93 (CI 95% 0.75 — 1.15) Based on data from 9,285 participants in 6 studies.	**40** per 1000 Difference:	**37** per 1000 **3 fewer per 1000**	**High**	There is little to no effect of antibiotics on serious adverse events

Outcome Timeframe	Study results and measurements	Comparator No antibiotics	Intervention Antibiotics	Certainty of the evidence (Quality of evidence)	Summary
			(CI 95% 10 fewer — 6 more)		

2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**

3.7 Rehabilitation for patients with COVID-19

At the outset of the pandemic, the rehabilitation needs for patients recovering from COVID-19 were based on evidence from the critical care population and long-term sequelae in SARS-CoV-1 survivors *(298)(299)(300)(301)(302)(303)(304)(305)(99)(306)(307)(308)*. Post-intensive care syndrome (PICS) refers to a range of impairments including physical deconditioning, and cognitive and mental health impairments. The COVID-19 patients who are at higher risk of ICU admission are also those at higher risk to develop PICS, i.e. older persons with underlying diseases such as diabetes, hypertension, increased frailty and other chronic disorders *(309)*. Intensive care unit-acquired weakness is ubiquitous in ARDS survivors, as it is in critically ill COVID-19 patients who required prolonged sedation *(100)*, and recovery may be incomplete at 5 years after ICU discharge *(310)*. Some studies suggest that cognitive impairment ranges from 70–100% at hospital discharge, 46–80% at 1 year, and 20% at 5 years. Mood disorders including depression and PTSD are also sustained and prevalent *(310)*. For ARDS survivors, a reduced exercise capacity persists in the context of relatively preserved pulmonary function at 1 year *(311)*. In SARS-CoV-1 survivors, pulmonary function at 1-year is reported to be normal in 63%, mildly reduced in 32% and moderately impaired in 5%, with abnormalities characterized by restrictive patterns and reduced carbon monoxide diffusing capacity *(312)*.

The following symptoms have been reported 4–8 weeks after discharge from the hospital in both ICU admitted COVID-19 patients and non-ICU admitted COVID-19 patients: new illness-related fatigue, breathlessness, PTSD symptoms, pain, voice change, cough, dysphagia, anxiety, depression, and problems with concentration, memory and continence. Patients admitted to ICU had greater prevalence of symptoms in almost all reported symptom domains than COVID-19 patients not admitted to ICU *(313)*. More than half of all COVID-19 patients who had been hospitalized, regardless of their clinical management, reported persistence of fatigue at 60 days since the onset of symptoms *(313)(314)*.

With progression of the pandemic and the follow up of patients who have not been critically ill, new evidence is emerging about COVID-19 related persistent symptoms, which have parallels with other coronavirus diseases. Some patients with SARS-CoV-1 infection went on to develop a long-term illness with widespread pain, fatigue, depression and sleep disturbance *(315)(205)*. PTSD has also been described after SARS-CoV-1 infection *(205)(205)*.

Early findings report, most commonly reported ongoing symptoms (regardless of hospitalization status) are fatigue, muscle ache, shortness of breath and headache at a follow up of 4 months *(316)*. Not returning to usual health within 2–3 weeks of testing was reported by approximately one third of symptomatic adults in an outpatient setting *(317)*. A study reported that at 3 months after the onset of symptoms, one third of non-hospitalized patients were to some degree dependent on others for personal care *(318)*.

In addition, several complications from COVID-19 have been reported in different clinical domains, resulting from a thrombotic event (such as ischaemic stroke and ischaemic heart disease), direct invasion (such as myocarditis, myositis, and meningitis) or an immune-mediated reaction (such as Guillain-Barré syndrome). While many of these complications are amenable for rehabilitation, they are not addressed in this chapter. Clinicians and rehabilitation professionals can refer to existing clinical practice guidelines for the appropriate management of these sequelae.

Patients with COVID-19, should be provided with education and support for the self-management of breathlessness and resumption of activities, both in a hospitalized and a non-hospitalized setting caring for COVID-19 *[Non-GRADE based recommendation].*

Remarks:
1. Education about control of breathing can support COVID-19 patients to those recovering from respiratory illness, especially those troubled by breathlessness. Patients may be advised to adopt positions, such as high side lying and forward lean sitting, and breathing techniques, such as pursed lip breathing and square box breathing, that help to manage breathlessness. Adequate walking pace regulation is recommended to reduce breathlessness and to prevent desaturation on exertion. Severe shortness of breath that is not relieved by positioning and breathing techniques requires medical investigation.
2. All rehabilitating patients should be educated about resuming everyday activities conservatively at an appropriate pace that is safe and manageable for energy levels within the limits of current symptoms and should not be pushed for post-exertional fatigue. A gradual increase in exercise should be based on symptoms.
3. For patients with COVID-19 that also have underlying cardiovascular or pulmonary conditions, resumption of exercise should be done after consultation with appropriate health professionals (239)(108)(65). COVID-19 patients with confirmed cardiac involvement need a cardiac evaluation before resuming exercise.
4. Resuming sports gradually should also be guided by appropriate health professionals, an example is provided for return-to-play guideline for myocarditis (239)(108)(65).

3.8 Caring for women with COVID-19 during and after pregnancy

The results of a living systematic review (as of 27 April 2021) (39) show that the odds of stillbirth (OR= 1.81, 95% CI 1.38 to 2.37; 25 studies, 423 477 women) and neonatal death (OR= 2.35, 95% CI 1.16 to 4.76; 21 studies, 12 416) were higher in babies born to women with Covid-19 versus those without Covid-19. Although the overall number of neonatal deaths was small (only sixteen events in the Covid-19 group), pregnant women with COVID-19 are more likely to experience any type of preterm birth (OR=1.57, 95% CI 1.36–1.81; 48 studies, 449 040 women) compared with pregnant women without the disease. Overall, 25% (95% CI 21% to 30%; 97 studies, 17 687 women) of neonates were admitted to the neonatal intensive care unit, and had higher odds of NICU admission (OR= 2.18, 95% CI 1.46 to 3.26; 29 studies, 197 196 neonates)

In another living systematic review (as of 3 August 2021) *(328)* SARS-CoV-2 positivity rates were found to be low in babies born to mothers with SARS-CoV-2 infection (1.8%, 95% CI 1.2% to 2.5%; 140 studies, 14 271 babies); the rates are lower (1%) when limited to babies with antenatal or intrapartum exposure to the virus. Evidence was found for confirmed mother-to-child transmission through in utero, intrapartum, and early postnatal exposure; but the overall risk is likely to be low. Severity of maternal Covid-19 (OR=2.36, 95% CI 1.28 to 4.36; 22 studies, 2842 mother-baby dyads) and maternal admission to an intensive care unit (3.46, 95% C 1.74 to 6.91; 19 studies, 2851 mother-baby dyads) seem to be associated with SARSCoV- 2 positivity in offspring, and not trimester of maternal infection, gestation at birth, mode of delivery, breastfeeding, or mother-baby dyad separation at birth.

This section builds on existing recommendations from WHO on pregnancy and infectious diseases and provides additional remarks for the management of pregnant and recently pregnant women.

Pregnant or recently pregnant women with suspected or confirmed mild or moderate COVID-19 may not require acute care in hospital, unless there is concern for rapid deterioration or an inability to promptly return to hospital; but isolation to contain virus transmission is recommended, and can be done at a health facility, community facility or at home, according to established COVID-19 care pathways *[Non-GRADE based recommendation].*

Remarks:

1. Counsel pregnant and recently pregnant women about maternal and newborn signs, including COVID-19 danger signs and maternal perception of decreased fetal movements, and advise them to seek urgent care if they develop any worsening of illness or other danger signs, such as danger signs of pregnancy (including: bleeding or leaking fluid from the vagina, blurry vision, severe headaches, weakness or dizziness, severe abdominal pain, swelling of face, fingers, feet, inability to tolerate foods or liquids, convulsions, difficulty in breathing, decrease in fetal movements). Update birth preparedness and complication readiness plans so they know when and where to seek care.
2. In pregnant and postnatal women that are being cared for at home in self-isolation, self-care interventions should be encouraged. Routine antenatal or postnatal health visits in health facilities should be postponed, and delivery of antenatal and postnatal counselling and care, should instead be conducted via alternative platforms such as home-based, phone or telemedicine (329)(330). If postponed, health visits should be rescheduled until after the period of self-isolation following national guidelines and advice, and in consultation with the health care provider. For women requiring abortion services, consider alternative modes of service delivery, including self-management of medical abortion up to 12 weeks' gestation, where women have access to accurate information and to a health care provider at any stage of the process. Postponing abortion care may lead to increased morbidity and mortality where individuals resort to unsafe abortion practices as abortion service delivery is time-bound by gestational limits prescribed by the law. See the WHO Consolidated guideline on self-care interventions for health (113) and WHO Abortion Care Guideline (331)
3. Counsel women about healthy diet, mobility and exercise, intake of micronutrients for herself and her infant, tobacco use and second-hand smoke exposure, use of alcohol and other substances, as per WHO guidelines on antenatal and postnatal care. Clinical enquiry about the possibility of gender-based violence should be strongly considered, where there is the capacity to provide a supportive response (including referral where appropriate) and where the WHO minimum requirements are met. See resource (330).
4. When caring for pregnant and recently pregnant women with underlying NCDs or pregnancy-induced conditions (e.g. gestational diabetes, pregnancy-induced hypertension) continue or modify previous medical therapy according to the woman's clinical condition.

3.9 Feeding and caring for infants and young children of mothers with COVID-19

Relatively few cases have been reported of infants confirmed with COVID-19; those that have been reported experienced mild illness. Of 115 mother-child pairs from 17 articles where the mother is confirmed to be infected with COVID-19, 13 children had COVID-19 (4 breastfed, 5 formula-fed, 2 mix-fed, 2 unreported feeding practice). Twenty mothers had breastmilk samples tested for the presence of SARS-CoV-2 RNA particles by RT-PCR; 7 of them had children with COVID-19 (2 breastfed,1 formula fed, 2 mix-fed, 2 unreported). Of the 20 with breastmilk tested, 18 had negative results and 2 had positive results. One of the two mothers whose breastmilk sample was positive for SARS-CoV-2, had a mix-fed child who was not infected with COVID-19; the other one had a child with COVID-19 (feeding practice was not reported) *(115)(334)(335)(336)(337)(338)(339)(340)(341)(342)*.

Breastfeeding protects against morbidity and death in the post-neonatal period and throughout infancy and childhood. The protective effect is particularly strong against infectious diseases that are prevented through both direct transfer of antibodies and other anti-infective factors and long-lasting transfer of immunological competence and memory. See WHO *Essential newborn care and breastfeeding (343).* Therefore, standard infant feeding guidelines should be followed with appropriate precautions for IPC.

Recommendations on the care and feeding of infants whose mothers have suspected or confirmed COVID-19 promote the health and well-being of the mother and infant. Such recommendations must consider not only the risks of infection of the infant with the COVID-19 virus, but also the risks of serious morbidity and mortality associated with not breastfeeding or the inappropriate use of breastmilk substitutes as well as the protective effects of skin-to-skin contact and kangaroo mother care. In light of the current evidence, WHO has concluded that mothers with suspected or confirmed COVID-19 should not be separated from their infants. Mother-infant contact and holding enhances thermoregulation and other physiological outcomes, significantly reduces mortality and morbidity, and improves child and parental attachment. Overall, the recommendation to keep mothers and their children together is based on several important benefits that outweigh the potential (and likely mild) harms of COVID-19 transmission to the child.

We recommend that mothers with suspected or confirmed COVID-19 should be encouraged to initiate and continue breastfeeding. From the available evidence, mothers should be counseled that the benefits of breast-feeding substantially outweigh the potential risks of transmission *[Non-GRADE based recommendation]*.

Remarks:

1. WHO recognizes that the recommendation for an infected mother to be in close contact with her baby may appear to contradict other IPC measures that include isolation of persons infected with COVID-19 virus (165). However, the balance of risks is significantly different for infants than for adults. In infants, the risk of COVID-19 infection is low, the infection is typically mild or asymptomatic, and the consequences of not breastfeeding or separation of mother and child can be significant. At this point it appears that COVID-19 in infants and children represents a much lower risk to survival and health than the other infections and conditions that breastfeeding is protective against. This protection is especially important when health and other community services are themselves under pressure. In contrast, the risks associated with COVID-19 in adults are much higher and more severe. Improved communication is needed to address the uncertainties and confusion among programme managers, health workers and communities on this issue.
2. See Table 21.1 below for recommendations when mother with COVID-19 is caring for infant.

Info Box

Table 21.1. Summary of recommendations when mother with COVID-19 is caring for infant

	Interventions
Mother infant contact at birth	Mothers should not be separated from their infants unless the mother is too sick to care for her baby. If the mother is unable to care for the infant another competent family caregiver should be identified. Mother and infant should be enabled to remain together while rooming-in throughout the day and night and practise skin-to-skin contact, including kangaroo mother care, especially immediately after birth and during establishment of breastfeeding, whether they or their infants have suspected or confirmed COVID-19 virus infection. Neonates born to mothers with suspected or confirmed COVID-19 should be breastfed within 1 hour of birth. Mothers should apply appropriate IPC. Early and uninterrupted skin-to-skin contact between mothers and infants should be facilitated and encouraged as soon as possible after birth, while applying necessary measures for IPC. This applies also to infants who are born preterm or low birth weight. If the newborn or infant is ill and requires specialist care (such as neonatal unit), arrangements should be made to allow the mother free access to the unit, with appropriate IPC measures. Earlier initiation of breastfeeding results in greater benefits. This may be relevant to mothers who give birth by caesarean section, after an anaesthetic, or those who have medical instability that precludes initiation of breastfeeding within the first hour after birth.
During early childhood	Infants should be breastfed exclusively during the first 6 months after birth, as breastmilk provides all the nutrients and fluids they need. From 6 months of age, breastmilk should be complemented with a variety of adequate, safe and nutrient-dense foods. Breastfeeding should continue up to 2 years of age or beyond. Breastfeeding counselling, basic psychosocial support and practical feeding support should be provided to all pregnant women and mothers with infants and young children if they or their infants and young children have suspected or confirmed COVID-19 infection.
If feeding is interrupted	In situations when severe illness in a mother prevents her from caring for her infant or prevents her from continuing direct breastfeeding, mothers should be encouraged and supported to express milk, and the breastmilk provided safely to the infant, while applying appropriate IPC measures. In the event that the mother is too unwell to breastfeed or express breastmilk, explore the viability of feeding with donor human milk. If this is not possible, consider wet nursing (defined as another woman breastfeeds the child) or appropriate breastmilk substitutes, informed by feasibility, safety, sustainability, cultural context, acceptability to mother and service availability. Mothers who are not able to initiate breastfeeding during the first hour after delivery should still be supported to breastfeed as soon as they are able. Assistance should be provided after recovery for relactation to re-establish a milk supply and continue breastfeeding.
Practices the mother should perform during all infant and childcare	Perform frequent hand hygiene with soap and water or alcohol-based hand rub, especially before contact with her child. Perform respiratory hygiene: sneeze or cough into a tissue and immediately dispose of the tissue. Hands should immediately be washed with soap and water or alcohol-based hand rub. Clean and disinfect surfaces with which the mother has been in contact.

	Wear a medical mask until symptom resolution and criteria for release from isolation have been met. Additionally, breastfeeding mothers should be helped to clean her chest with soap and water if she has been coughing on it before breastfeeding. She does not need to wash her breasts prior to every breastfeed. While mothers are recommended to wear medical masks, if the mother does not have a medical mask, she should still be encouraged to continue breastfeeding as the benefits of breastfeeding outweigh the potential risks of transmission of the virus when breastfeeding while applying other IPC measures.
Best practices for breast-feeding	Health facilities providing maternity and newborn services should enable a mother to breastfeed for as often and for as long as she wishes. Minimizing disruption to breastfeeding will require health care practices that enable a mother to breastfeed. All mothers should receive practical support to enable them to initiate and establish breastfeeding and manage common breastfeeding difficulties. This support should be provided by appropriately trained health care professionals and community-based lay and peer breastfeeding counsellors. There should be no promotion of breastmilk substitutes, feeding bottles and teats, pacifiers or dummies in any part of facilities providing maternity and newborn services, or by any of the staff. Health facilities and their staff should not give feeding bottles and teats or other products that are within the scope of the International Code of Marketing of Breast-milk Substitutes and its subsequent related WHA resolutions, to infants. If the mother is too unwell to breastfeed or express breastmilk, explore the best alternatives to breastfeeding a newborn or young infant, in priority order, as follows: 1) donor human milk should be fed if available from a human milk bank; 2) if supplies are limited, prioritize donor human milk for preterm and low birthweight newborns; 3) wet nursing may be an option depending on acceptability to mothers and families, availability of wet nurses and services to support mothers and wet nurses. COVID-19 testing of a woman who is a potential wet nurse is not required. Prioritize wet nurses for the youngest infants. In settings where HIV is prevalent, prospective wet nurses should undergo HIV counselling and rapid testing where available. In the absence of testing, if feasible, undertake HIV risk assessment. If HIV risk assessment or counselling is not possible, facilitate and support wet nursing; 4) breastmilk substitutes may be used as a last resort.

3.10 Caring for older people with COVID-19

Older age has been reported as a risk factor for increased mortality in those affected by COVID-19. Other risk factors that have been reported are: smoking, diabetes, hypertension, cardiovascular, cancer, chronic lung disease, and functional decline *(344)(345)(346)*. Since older people are often affected by these conditions, they are potentially at the highest risk for fatality. Furthermore, the majority of long-term care service users are older people with multiple underlying conditions and weak immune systems, which make them more susceptible to severe COVID-19 and poor outcomes *(116)*. Refer to the WHO policy brief *Preventing and managing COVID-19 across long-term care services (116)* and WHO guidance *Integrated care for older people (ICOPE) (347)* for person-centred and coordinated model of care.

3.11 Palliative care and COVID-19

Palliative care is a multifaceted, integrated approach to improving the quality of life of adults and paediatric patients and their families facing the problems associated with life-threatening illness such as COVID-19. Palliative care focuses on prevention and relief of suffering by means of early identification, assessment and treatment of physical, psychosocial and spiritual stressors. Palliative care includes but is not limited to end-of-life care *(352)*. Palliative interventions should be integrated with curative treatment *(352)*. Basic palliative care, including relief of dyspnoea or other symptoms and social support, should be practised by all doctors, nurses, social workers and others caring for persons affected by COVID-19, adult or child *(352)(353)*. Refer to the WHO guide Integrating palliative care and symptom relief into responses to humanitarian emergencies and crises *(352)*.

3.12 Care of COVID-19 patients after acute illness

New evidence is emerging about COVID-19 related persistent symptoms, which have parallels with other coronavirus diseases *(315)*.

The clinical characterization of mid- and long-term effects of COVID-19 remain to be clearly described and understood. In hospitalized patients, ICU and non-ICU, there are reports of new illness-related fatigue, breathlessness, PTSD symptoms, pain, voice change, cough, dysphagia, anxiety, depression, and problems with concentration, memory and continence. Patients admitted to ICU had greater prevalence of symptoms in almost all reported symptom domains than COVID-19 patients not admitted to ICU *(313)*. As well, more than half of all COVID-19 patients who had been hospitalized, regardless of their clinical management, reported persistence of fatigue at 60 days since the onset of symptoms *(313)(314)*.

Early findings report, most common ongoing symptoms (regardless of hospitalization status) are fatigue, muscle ache, shortness of breath and headache at a follow up of 4 months *(316)*. Not returning to usual health within 2–3 weeks of testing was reported by approximately one third of symptomatic adults in an outpatient setting *(317)*. A study reported that at 3 months after the onset of symptoms, one third of non-hospitalized patients were to some degree dependent on others for personal care *(318)*.

3.12.1 Follow-up care

Good practice statement

Patients who have had suspected or confirmed COVID-19 (of any disease severity) who have persistent, new, or changing symptoms should have access to follow-up care *[Good practice statement]*.

Remarks:

Recognition

- *All patients (and their caregivers) with COVID-19 should be counselled to monitor for resolution of signs and symptoms. If any one or more of these persist, or patients develop new or changing symptoms, they should seek medical care according to national (local) care pathways.*
- *This includes counselling about acute life-threatening complications, such as pulmonary embolism, myocardial infarction, dysrhythmias, myopericarditis and heart failure, stroke, seizures and encephalitis (354)(126), for which they should seek emergency care.*
- *Patients with severe and critical COVID-19 may develop post-intensive care syndrome (PICS), with a range of impairment including (but not limited to) physical deconditioning, respiratory, swallow, cognitive, and mental health symptoms. See Chapter 19. Rehabilitation for patients with COVID-19 for more details on PICS.*

Management

- *National (local), coordinated care pathways should be established that can include primary care providers (i.e. general practitioners), relevant specialists, multidisciplinary rehabilitation professionals, mental health and psychosocial providers, and social care services.*
- *Management should be tailored according to patient needs and be coordinated.*
- *Management interventions include addressing promptly life-threatening complications. For non-life-threatening complications, management may entail education, advice on self-management strategies (i.e. breathing techniques, pacing), caregiver support and education, peer-to-peer groups, stress management, stigma mitigation and home modification; prescription of rehabilitation programmes, and/or specialty management.*
- *See Chapter 19. Rehabilitation for patients with COVID-19 for recommendations regarding screening, assessment and rehabilitation interventions to facilitate onward referrals for inpatient, outpatient, or community-based follow up, to ensure continuity during transitions of care.*

Evidence to decision

Values and preferences

No substantial variability expected

Applying the agreed values and preferences, the GDG inferred that well-informed patients would consider the possible harms associated with COVID-19 follow-up to be negligible, and that ensuring access to care is an important value to consider. To this end, WHO has developed and released a clinical case definition of

post COVID-19 condition, also known as “Long COVID-19” by a Delphi consensus, 6 October 2021 to help guide patients, caregivers, and health workers on how to identify individuals who are affected by this condition.

Resources and other considerations

Important considerations

National (local), coordinated care pathways should be established that can include primary care providers (i.e. general practitioners), relevant specialists, multidisciplinary rehabilitation professionals, mental health and psychosocial providers, and social care services. Alternative delivery platforms such as home-based phone, telemedicine, or community outreach teams may be used.

Justification

Applicability

Special populations

Considerations should be made when following up special populations such as children and young people, pregnant women, and older persons (see Section 22 Caring for older people with COVID-19), and their caregivers.

Research needs

Priority areas of research include:

- Natural history (clinical characteristics, risk factors, association with disease severity and differences between high-income and lower middle-income settings);
- Pathophysiology (viral persistence, immune dysregulation, thrombosis etc.);
- Impact of vaccination;
- Impact of treatments.

3.12.2 Rehabilitation of adults with post COVID-19 condition

WHO guidelines for the management of patients with post-COVID-19 condition are in preparation. This section will be migrated to the new guideline when it is available.

Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Symptoms may be new onset following initial recovery from an acute COVID-19 episode, or persist from the initial illness period (WHO clinical case definition). Symptoms and impairments can present as either clusters or isolated symptoms, that limit daily activities and restrict social participation. Symptoms may be present for prolonged time frames and/or relapse over time.

This rehabilitation guidance has been developed for adults living with post COVID-19 condition and is targeting clinicians and programme planners. It has 16 topics covering both recommendations for rehabilitation programme planning and recommendations on clinical rehabilitation management. Impairment-specific topics have been selected by the GDG based on their prevalence in post COVID-19 condition and amenability to rehabilitation in other health conditions. In addition, five topics have been found essential for rehabilitation programme planning and model of care implementation.

As post COVID-19 condition can often have a multi-system impact on functioning, many of the impairment-specific topics may be interconnected and/or linked to support the rehabilitation process, reflecting the often clustered presentation of symptoms and impairments. Clinicians should take this into account to avoid duplication of interventions when developing an individualized rehabilitation care plan.

Topic 1 Components and functions of rehabilitation care

An organizational structure is required to deliver health services and interventions within a health system. This structure relies on multiple components that are required to support the delivery of services. Components also benefit from functions as mechanisms or tools to support the operationalization of the different components.

Conditional recommendation for

To support the delivery of rehabilitation services for post COVID-19 condition we suggest the following core components:

1. Multidisciplinary rehabilitation teams;
2. Continuity and coordination of care; and
3. People-centred care and shared decision-making.

To support the operationalization of the core components, planners could implement core functions, including:

1. Standardized symptoms assessment and outcome measurement;
2. Follow-up system; and
3. Referral system.

Practical info

Described components highlight the importance of interdisciplinary work and the involvement of people living with post COVID-19 condition with respect to preferred rehabilitation services and outcomes. Other components address the importance of rehabilitation needs assessment, education and guided self-management as integral parts of case management. The reported functions suggest rehabilitation care that is supported with a standardized monitoring system, including outcome measurement, which allows referrals based on patient needs and an option of home-based care that may be delivered with tele-rehabilitation services. The crux of implementing these recommendations will be the delivery of standardized training for selected staff within dedicated rehabilitation programmes.

There are currently no shared decision-making tools specifically designed for post COVID-19 condition. There is no defined core assessment for post COVID-19 condition to be used within rehabilitation care based on impact studies. Post COVID-19 condition subgrouping evidence will help define the most appropriate referral pathways and timing of follow-up.

Evidence to decision

Certainty of the evidence	A systematic scoping review for the model of rehabilitation care (Annex 8) only identified papers that have been based on expert evidence and no GRADE certainty of evidence assessment has been applied. There is currently no evidence on impact or cost-effectiveness of components and functions underlying rehabilitation care *(356)*. The recommendation is based on expert evidence.

Justification

A Cochrane Rehabilitation systematic scoping review identified 12 articles including information on components or functions for rehabilitation care. A total of 18 components were described. The most common components were multidisciplinary rehabilitation teams, continuity and coordination of care, people-centred care and shared decision-making, case management, evidence-based care, patient education, guided self-management, integrated care and patient needs assessment. The panel agreed on the first three components to constitute the recommendation. A total of nine functions were described. The most common functions were standardized symptoms assessment, follow-up system, referral system, telehealth/virtual care and home-based care. The panel agreed on the first three functions to constitute the recommendation, and added the standardized outcome measurement. We provide a working definition for the proposed components and functions in Annex 8.

We expect that guiding people living with post COVID-19 condition through rehabilitation care based on multidisciplinary rehabilitation teams, coordinated care and shared decision-making may improve quality of life, lead to better experience and engagement with care, and increase satisfaction with access to rehabilitation. In countries with limited access to rehabilitation structures, organizing care models based on these components could represent additional cost.

Topic 2 Red flags for safe rehabilitation

Assessment is essential to determine safe and effective rehabilitation *(357)*. In people with post COVID-19 condition in need of rehabilitation, this includes ruling out complications resulting from COVID-19 that require further investigation and management before a referral to rehabilitation in general or a specific rehabilitation intervention is undertaken *(357)(358)(128)*. Red flags for safe rehabilitation are those complications where commencing rehabilitation could cause an acute event or deterioration.

Strong recommendation for

In adults with post COVID-19 condition exertional desaturation and cardiac impairment following COVID-19 should be ruled out and managed before consideration of physical exercise training. While orthostatic intolerance and post-exertional symptom exacerbation (PESE) are amenable to rehabilitation, their presence will require interventions to be modified in view of these diagnoses for rehabilitation to be safe *[Strong recommendation]*.

Practical info

Exertional desaturation is more likely and should be particularly considered in the post-hospital cohort *(359)(360)*. Exertional desaturation may be suspected in the presence of dyspnoea on exertion. Exertional desaturation can be assessed with a locally available appropriate exercise test that includes measure of oxygen status (e.g. 1 minute sit to stand with pulse oximetry) *(357)*. Drop in pulse oxygen saturation of more than 3–4% from baseline measurements *(129)(131)(133)* or to 94% or below, on exercise test is considered desaturation. Exercise testing for exertional desaturation should be avoided or modified (within tolerable limits for the individual) in the presence of PESE *(361)*.

Cardiac impairment may be suspected in the presence of fast or difficulty in breathing, high resting or exertional heart rate, chest pain or palpitations *(362)*.

Post-exertional symptom exacerbation can be assessed through history taking and reporting of symptom patterns *(361)* (see topic Post-exertional symptom exacerbation). Orthostatic intolerance can be investigated by measuring heart rate and blood pressure in lying and prolonged standing with an active stand test *(357)* (see topic Orthostatic intolerance).

Red flags for safe rehabilitation may be unclear and depend on the clinical skills of the team and availability of diagnostic investigations. Clinical teams should have access to training to screen for and identify red flags *(135)*. Tests and investigations of red flags should be tailored to people's signs and symptoms to rule out and prevent life threatening complications *(357)*. No one set of investigations and tests would be suitable for everyone because of the wide range of symptoms and severity.

Evidence to decision

Certainty of the evidence	A systematic scoping review for the model of rehabilitation care including red flags for safe rehabilitation (Annex 8) only identified papers that have been based on expert evidence and no GRADE certainty of evidence assessment has been applied. The recommendation is based on expert evidence.

Justification

Exertional desaturation indicates possible new pulmonary conditions including but not limited to lung interstitial abnormality or pulmonary embolus *(363)(359)(364)(365)(365)(360)(366)*. Exertional desaturation warrants further investigation to understand etiology, exclude and manage significant underlying pathology, before rehabilitation can be commenced safely *(357)*. New cardiac impairment in post COVID-19 condition patients, for example myocarditis, ischaemic heart disease, left ventricular failure and arrythmia, has been reported in both previously hospitalized and non-hospitalized patients *(363)(364)(360)(362)(367)(368)(369)(370)(371)* and warrants further investigation *(372)(136)*. Commencing rehabilitation that increases oxygen demand, for example physical exercise training, in the presence of exertional desaturation or new cardiac impairment could precipitate an acute event.

Post-exertional symptom exacerbation and orthostatic intolerance require modifications to rehabilitation to prevent deterioration of symptoms *(373)(374)(361)* (see corresponding topics).

Topic 3 Referral principles

This topic provides guidance for programme planners and health workers on who is expected to benefit from entering a rehabilitation programme for post COVID-19 condition. This recommendation builds on patient level characteristics for referral, and timing of referral is considered.

Conditional recommendation for

An early referral of adults with post COVID-19 condition for appropriate rehabilitation services is suggested when experiencing symptoms and impairments that may be managed effectively and that have an impact on everyday functioning, when red flags for safe rehabilitation have been considered *[Conditional recommendation]*.

Practical info

The use of a tool to assess and measure the impact of post COVID-19 condition on an individual may be considered, either self-scored, or administered by a trained health worker. However, agreed post Covid-19 condition-specific measurement instruments of disability, functioning, and health are currently lacking, and challenges exist when applying patient-reported outcome measures (PROMs) developed for other conditions *(375)*. Some examples of condition-specific assessments are available in literature *(376)(377)* and countries have adapted the WHO Post COVID-19 CRF (which includes WHODAS 2.0, 12-item) to serve as a screening tool (e.g. Nepal). The Post COVID-19 Functional Status scale (PCFS) provides a validated numerical assessment of functional status for highly symptomatic patients at initial assessment and over time *(378)(379)*, which may need a counter check with physical examination.

An individualized assessment is suggested which preferably involves a physician to define underlying organ damage and to exclude red flag disorders prior to starting rehabilitation *(357)(362)(138)(140)(380)(381)*.

Evidence to decision

Certainty of the evidence	A systematic scoping review for the model of rehabilitation care including referral principles (Annex 8) only identified papers that have been based on expert evidence and no GRADE certainty of evidence assessment has been applied. The recommendation is based on expert evidence.
Resources and other considerations	Entrants to rehabilitation programmes should be willing and able to engage in the rehabilitation process. Referral routes may be via hospital, health centre, and community referral or self-referral *(138)(141)(376)*. Post COVID-19 condition affects people with varying combinations of impairments and therefore, experts value a personalized assessment to identify the impact of post COVID-19 condition upon the functioning of the individual, including activity limitations and social participation restrictions, and the development of a personalized rehabilitation programme.

Justification

People with post COVID-19 condition experiencing limitations in functioning *(357)(143)(138)(141)(145)(140)(147)(382)(149)* should be referred for rehabilitation. In post COVID-19 condition, several symptoms and impairment types occur which may be managed effectively by rehabilitation, such as fatigue, breathing impairment, cognitive impairment, orthostatic intolerance, PESE, swallowing impairment, voice impairment, joint pain, and olfactory impairment. Symptoms and impairments may impact everyday functioning in varying degree from limited to life-changing, and it has been reported that symptom scores strongly positively correlate with functional difficulty scores *(383)*. Impairments with a higher level of burden regarding everyday functioning are fatigue, breathlessness, memory and concentration problems, pain, and PESE *(384)(385)(386)(387)(388)(389)(390)(391)*.

The initial severity of COVID-19 *(149)*, and severity or clustering of particular symptoms or impairments should not impact referral for rehabilitation.

Upon diagnosis of post COVID-19 condition (new or persistent symptoms usually at 12 weeks following a confirmed or probable SARS-CoV-2 infection), an early referral into rehabilitation based on the above referral principles is suggested. Referral to rehabilitation before 12 weeks may be considered based on clinical guidance.

We do not yet have sufficient evidence of expected rehabilitation outcomes in people with post COVID-19 condition and subpopulations. However, maintenance or improvement of functioning is expected in patients who are referred using this recommendation based on the available indirect evidence for interventions for rehabilitation of selected impairments.

There may be large numbers of patients referred to rehabilitation services. As outcomes and interventions are developed, it is likely that referral criteria will become more specific.

Topic 4 Service delivery

Post COVID-19 condition is expected to pose continued burden on health care resources *(391)*. Therefore, it is essential for health services planners including rehabilitation programme planners, to consider instituting strategies within their settings to enhance care delivery and lessen health care resource consumption or burden.

Conditional recommendation for

For rehabilitation service delivery for post COVID-19 condition we suggest using a hybrid approach of in-person and remote models that is integrated across all levels of health care. It is suggested that the length of a rehabilitation programme is based on patient needs, enabling re-engagement if new onset functional decline occurs *[Conditional recommendation]*.

Practical info

SARS-CoV-2 infection prevention measures must continue to be applied during rehabilitation service delivery by both patients and health workers according to national guidance.

Self-management should be enabled and encouraged, including symptom monitoring and management at home *(392)(393)*. However, safety considerations should be factored in by equipping the patients, family, loved ones and their care providers with knowledge and skills on self-monitoring for symptom triggers and basic identification of danger signs and symptoms that may arise whilst undergoing at-home rehabilitation *(140)(385)(394)*.

Rehabilitation service delivery should be supported with training and psychological support of professionals. Health workers are at risk of work-related stress and burnout *(395)*, given the uncertainty experienced around treating a novel condition, and an absence of guidelines or care pathways *(396)*.

Evidence to decision

Certainty of the evidence	A systematic scoping review for the model of rehabilitation care including service delivery setting (Annex 8) only identified papers that have been based on expert evidence and no GRADE certainty of evidence assessment has been applied. The recommendation is based on expert evidence.

Justification

A hybrid in-person and remote model is suggested that is based on patient preference and needs over time, available resources to the health system and patients, and community transmission status *(140)(385)(397)(392)(396)*. In-person initial evaluation and follow up for post COVID-19 condition is preferred as it allows a more thorough symptom and physiological assessment.

Integrating rehabilitation into existing health services delivery is considered less involving in terms of health care organization than starting a parallel system, and is expected to be cost-effective *(140)(385)(396)(398)*. Post COVID-19 condition rehabilitation does not or should not require high-level resources. Post COVID-19 condition rehabilitation should be integrated across all levels of health care with appropriate investment in primary care level resources and training *(392)(396)(398)*.

The panel does not recommend on an ideal length of rehabilitation programme; patients present differently and have varying rehabilitation needs. Currently little is known regarding the effectiveness of interventions and their respective dosages. Therefore, current best practice would be to consider personalizing the duration of the rehabilitation episode based on the assessment and monitoring findings. In addition, symptoms may be labile or episodic and relapses often occur; having a viable option for re-evaluation and re-engagement with rehabilitation is important *(397)(392)(396)*.

It is expected that rehabilitation service delivery for post COVID-19 condition following a hybrid approach of in-person and remote models that is integrated across all levels of health care will result in most optimal outcomes. There is no published evidence to show that one type of service delivery setting is more or less likely to cause harm. The key safety factor is ensuring training of staff.

Topic 5 Workforce

Workforce planning is important to ensure that appropriate health care is provided effectively and efficiently. Adequate rehabilitation workforce planning for post COVID-19 condition is essential to improve or optimize the level of functioning of people experiencing persistent symptoms following SARS-CoV-2 infection *(140)*.

Conditional recommendation for

A workforce for the rehabilitation of adults with post COVID-19 condition may include but is not limited to physiotherapists, occupational therapists, nurses, psychologists, speech and language therapists, physicians and social workers. Community health care workers may be required based on local needs *[Conditional recommendation]*.

Practical info

Rehabilitation of people with post COVID-19 condition requires a well led, coordinated and transdisciplinary team with a range of health care professionals, which may need support from other services, community health care workers and volunteers.

A senior, experienced rehabilitation worker should be identified to comprehensively assess rehabilitation needs, and identify those occupational groups required for the rehabilitation care, support, and guidance on self-management of individual patients and their family, and to coordinate step-down processes. This person needs to be familiar with locally available resources.

For low-resource settings in which identified rehabilitation workforce is not available, we value task sharing between health care workers who have undergone training on safe rehabilitation.

Evidence to decision

Certainty of the evidence	A systematic scoping review for the model of rehabilitation care including workforce (Annex 8) only identified papers based on expert evidence and no GRADE certainty of evidence assessment has been applied. Limited evidence prevents identification of a core team of health care professionals providing interventions for rehabilitation of post COVID-19 condition. There is no data on the impact or cost-effectiveness of currently proposed rehabilitation workers for post COVID-19 condition. The recommendation is based on expert evidence.

Justification

A broad range of rehabilitation workers *(380)* are required as the symptoms and impairments in post COVID-19 condition result in limitations in functioning in physical, cognitive, communication, and mental domains, activity limitations and participation restrictions, and reduced well-being *(356)*. A single specialty perspective appears sub-optimal for the rehabilitation of people living with post COVID-19 condition and a transdisciplinary approach is likely the most beneficial to promote rehabilitation outcomes.

Rehabilitation workers aim to have a positive impact on the patient's everyday functioning, participation (including restrictions on employment and education), and the patients' and their carers' well-being. In the absence of natural recovery in people with post COVID-19 condition, it is anticipated that patients would benefit from rehabilitation services provided by the aforementioned workforce.

Topic 6 Post-exertional symptom exacerbation

Post-exertional symptom exacerbation (PESE), also referred to as post-exertional malaise (PEM), is defined as the worsening of symptoms that can follow minimal cognitive, physical, emotional, or social activity, or activity that could previously be tolerated *(150)*. Symptoms typically worsen 12 to 72 hours after activity and can last for days or even weeks, sometimes leading to a relapse *(150)(152)(399)(155)*. PESE can contribute to the episodic nature of disability in post COVID-19 condition, often presenting as unpredictable fluctuations in symptoms and function *(156)(158)*.

Conditional recommendation for

For the clinical rehabilitation management of PESE in adults with post COVID-19 condition we suggest using education and skills training on energy conservation techniques such as pacing approaches. The provision and training in the use of assistive products and environmental modifications may be useful for people experiencing moderate to severe PESE *[Conditional recommendation]*.

Practical info

Evidence-based questionnaires and screening tools *(155)(400)(401)(402)(160)(403)*, and patient-reported outcome measures *(404)(405)*, can be used to identify, assess, and monitor interventions for PESE.

Post-exertional symptom exacerbation may not be mentioned spontaneously by individuals, due to unfamiliarity with the concept *(400)*. Clinicians should carefully assess for PESE in post COVID-19 condition, including PESE symptoms, triggers, duration, and change over time *(403)*, while ruling out activity intolerance or reduced exercise tolerance which may be caused by respiratory, cardiovascular, and musculoskeletal conditions *(361)(382)(406)*.

Activity and energy management, or pacing, should be flexible, balancing activities and rest contingent on symptoms *(361)*. Pacing is itself a complex and active intervention, where physical and cognitive exertion, including over exertion, can be triggers for post COVID-19 condition symptom exacerbation or relapse *(388)(407)(408)(409)*.

Sustained symptom stabilization may suggest positive effects of pacing, and stability (e.g. 1 month) should be achieved before attempting to modify or increase activities *(361)*. Help patients to identify the timing to safely resume progressive and adapted physical activities. Interventions for rehabilitation based on fixed incremental increases in the time spent being physically active or graded exercise, should not be offered to people experiencing PESE *(150)*. Careful monitoring of symptoms over time can help identify symptom improvements, potential recovery, flare-ups, or relapses.

Evidence to decision

Certainty of the evidence

No direct evidence based on effectiveness studies for rehabilitation of PESE in post COVID-19 condition is yet available (Annex 6). Hence, no GRADE certainty of evidence assessment has been applied. Also, no Cochrane systematic review on the rehabilitation management of PESE has been identified (Annex 7, Exercise intolerance map). The recommendation is based on expert evidence and patient preferences, and is following guidance for PESE in other health conditions, which has been based on very low certainty of evidence *(150)*.

Justification

Interventions for rehabilitation of PESE include education about the importance of quality rest and sleep, and skills training on energy conservation techniques such as techniques for activity and energy management or pacing, techniques for building rest into routines effectively, developing an activity and energy management plan, establishing an individual activity pattern within current activity and energy limits that minimizes symptoms, and heart rate monitoring *(361)(150)(410)(406)(411)(412)(413)(414)*. Discuss and agree self-management strategies to respond promptly to a flare-up or relapse, such as identifying possible triggers, temporarily reducing activity levels, monitoring symptoms over time, and not returning to usual activity levels until the flare-up has resolved *(150)*.

The provision and training in the use of assistive products and environmental modifications aim to reduce activity limitations, optimize independence with daily activities impacted by PESE, and mitigate frequency of relapses (see topic Return to everyday activities and work). Patients with moderate (reduced mobility and restricted in all daily activities) or severe PESE (housebound and dependent on help for all daily activities) may benefit from walking canes or sticks, wheelchairs, and home adaptations for toileting.

Currently, there is no evidence to support one intervention over the other for PESE in post COVID-19 condition.

Energy conservation techniques are considered safe *(361)(410)(406)(411)(400)(415)*, and no evidence suggests risk of harm.

Topic 7 Arthralgia

Arthralgia in post COVID-19 condition presents as an inflammatory type of pain in one or more joints which may be dull, sharp, stabbing, shooting, burning, throbbing or aching (and excludes chest pain from costochondritis and pain of mechanical origin such as shoulder pain from prone positioning or low back pain). Arthralgia may appear suddenly or slowly develop with worsening progression and ranges in intensity from mild to severe. It may occur after the onset of fever and respiratory symptoms with the knee, ankle, and wrist joints most frequently affected, and seems to correlate with disease severity with possibility of poly-arthralgia *(416)(417)(162)(164)(166)(168)(170)*. It has been reported that infection with SARS-CoV-2 may be triggering reactive arthritis or short- or long-term autoimmune-mediated responses *(162)(166)(171)(172)(174)(418)(419)(420)(421)*.

Conditional recommendation for

For the clinical rehabilitation management of arthralgia in adults with post COVID-19 condition we suggest using a combination of pain education, skills training on self-management strategies, prescription of short-term anti-inflammatory drugs, and in the absence of PESE physical exercise training *[Conditional recommendation]*.

Practical info

Excluding PESE before commencing exercise therapy, and careful monitoring for PESE both during and after exercise, should be considered *(361)*.

Physical exercise training should be adapted to the patient (e.g. pregnant women, older people).

Evidence to decision

Certainty of the evidence	No direct evidence based on effectiveness studies for rehabilitation of arthralgia in post COVID-19 condition is yet available (Annex 6). Hence, no GRADE certainty of evidence assessment has been applied. Physical exercise training has been suggested based on low to moderate quality of evidence in other health conditions (Annex 7, Arthralgia map).

Justification

Patient education about the nature and pattern of pain improves understanding, builds confidence, empowers knowledge, and reduces fear of movement. Skills training on self-management strategies promote active joint movement within the limits of pain to prevent chronic pain from disuse and deconditioning *(422)(423)*.

Short-term low-dose corticosteroids *(174)(424)* or short-term non-steroidal anti-inflammatory drugs (NSAID) at an early stage *(162)(166)(171)(419)(425)(175)* may alleviate joint pain and improve physical function. Prescription should take into consideration contraindications such as uncontrolled hypertension and uncontrolled hyperglycaemia and potential adverse effects such as hyperglycaemia and hypernatraemia for corticosteroids, and risks to fetus or breastfed newborn or child for NSAID. There is no evidence to support one drug over the other in post COVID-19 condition, and selection should be based on contraindications and potential adverse effects.

Physical exercise training and aquatic exercises in various modalities have positive effects on joint pain, physical function, and quality of life *(426)(427)(428)(429)(430)(431)*.

Currently, there is no evidence to support one intervention over the other in post COVID-19 condition.

These interventions have clinically relevant effects on patient-reported pain, physical function and quality of life in health conditions with joint pain. Insignificant minor adverse effects have been reported with exercises in other health conditions *(430)(431)*.

Topic 8 Breathing impairment

Dyspnoea, also referred to as breathlessness or shortness of breath, is a subjective, distressing sensation of awareness of difficulty with breathing *(432)*. In post COVID-19 condition, this may occur at rest or on exertion, be constant, transient, or fluctuating, and can change in nature over time *(128)*.

Conditional recommendation for

For the clinical rehabilitation management of breathing impairment in adults with post COVID-19 condition we suggest using a combination of education and skills training on self-management strategies such as nasal breathing and pacing approaches and, in the absence of PESE, physical exercise training. Breathing control techniques could be offered to those presenting with a suboptimal breathing pattern, and psychological support may be useful to address contributing factors such as anxiety *[Conditional recommendation]*.

Practical info

Breathlessness may be investigated using an exercise tolerance test suited to the person's ability, for example the one-minute sit-to-stand test *(177)(433)(434)*. Rate of perceived exertion and heart rate may be useful monitoring parameters *(398)(435)*. Borg dyspnoea scale or MRC breathlessness scale could be used to assess and monitor the effectiveness of rehabilitation interventions for breathing impairment *(398)(436)(437)(438)(439)*.

Excluding PESE before commencing exercise therapy, and careful monitoring for PESE both during and after exercise, should be considered *(361)*.

Physical exercise training should be adapted to the patient (e.g. pregnant women, older people).

Evidence to decision

Certainty of the evidence

The certainty of direct evidence has been graded very low for all comparisons evaluated except for unsupervised home exercise programme when compared with educational instructions (low certainty) (Annex 6, dyspnoea PCC interventions). The interventions in the recommendation have been proposed considering evidence for interventions for rehabilitation of breathing impairment in other health conditions as well as expert evidence. The current quality of evidence for physical exercise training in other chronic health conditions is low to moderate (Annex 7, Dyspnoea map).

Justification

Education and skills training on self-management strategies are given on managing breathlessness with nasal breathing and pacing, with no evidence in post COVID-19 condition to support one over the other *(177)(440)*.

Physical exercise training should be personalized and tailored towards the patient's individual needs and adapted and titrated according to symptoms and assessment outcomes *(361)*. A physical exercise training programme may consist of muscle strengthening exercises and aerobic exercises, yoga or tai chi *(398)(177)(441)(442)(443)*, with no evidence in post COVID-19 condition to support one over the other. A combination of muscle strengthening exercises and aerobic exercises has demonstrated to reduce breathlessness and to improve exercise capacity in people with post COVID-19 condition *(444)(445)*.

Breathing control techniques consisting of breathing pattern retraining or diaphragmatic breathing could be offered to those presenting with a suboptimal breathing pattern *(398)(446)(441)* at rest and on exertion. Avoid anarchic ventilation by proposing apnoea exercises or timing the speaking time without inspiration.

Psychological support including stress management could be offered to patients to address factors contributing to dyspnoea, for example anxiety *(440)*. This should be offered regardless of pre-existing mental health conditions.

Currently, there is no evidence to support one intervention over the other in post COVID-19 condition.

The expected outcome of breathing control techniques is an improvement in breathing pattern *(446)* and improvement of breathlessness at rest, when speaking and on exertion *(361)*. Expected outcome of physical exercise training is reduced breathlessness and increased exercise tolerance *(442)(444)(445)*. The panel estimates that following psychological support, an improvement in the psychological well-being, increased ability to self-manage symptoms and improvement in experience of dyspnoea can be expected *(440)*.

Topic 9 Cognitive impairment

Post COVID-19 condition cognitive impairments are associated with alertness, attention, memory encoding, verbal fluency and executive function *(389)(447)(448)(449)(450)(451)(452)(453)(454)*. Problems with cognitive functions may comprise of fluctuating concentration, forgetfulness, word finding, problem solving and reasoning difficulties, and associated difficulty in participation in activities of daily living.

Conditional recommendation for

For the clinical rehabilitation management of cognitive impairment in adults with post COVID-19 condition we suggest using a combination of education, skills training on self-management strategies and cognitive exercises. The provision and training in the use of assistive products and environmental modifications may be useful to address the cognitive dysfunctions as they apply to daily functioning *[Conditional recommendation]*.

Practical info

Screening tools *(449)(450)(451)* and formal tests *(449)(451)(452)(453)* are used to identify and assess cognitive impairments. A set of harmonized procedures and methods for assessing neurocognitive functions in adults diagnosed with COVID-19 has been proposed *(455)*.

Cognitive deficits may overlap or present in clusters with other neurological and non-neurological deficits, including fatigue and mental health symptoms *(389)(178)(456)(457)*. These factors should be considered when assessing, planning for, and implementing an intervention (e.g. guidance on pacing to address fatigue), while considering pre-COVID-19 cognitive function (e.g. older people, people living with disabilities).

Subjective cognitive concerns on self-report inventories may not always be associated with objective cognitive deficits on formal testing or a history of SARS-CoV-2 infection. For some people, subjective concerns appear more closely linked to affective distress. This suggests that other interventions for rehabilitation (e.g. psychological support) may be appropriate for a subset of patients *(458)(459)(460)*.

Restorative and compensatory interventions may be implemented simultaneously and work reciprocally.

Interventions for rehabilitation of cognitive impairment should consider the episodic nature of post COVID-19 condition and anticipate possible relapses in cognitive functioning.

The interventions are focused on training both patients and caregivers to optimize cognitive function and/or to adapt the environment for successful interactions.

Evidence to decision

Certainty of the evidence	Limited data are available on rehabilitation for cognitive impairment in post COVID-19 condition *(442)(454)*. No RCT or non-randomized study of interventions (NRSI) with comparator have been identified for the rehabilitation management of cognitive impairment. Hence, no GRADE certainty of evidence assessment has been applied (Annex 6, Cognitive PCC interventions). The recommendation is based on large numbers of clinical studies among diverse patient populations that support rehabilitation for cognitive impairment *(179)*. The certainty of evidence for cognitive exercises is very low to high in patients with stroke, dementia, mild cognitive impairment and to maintain healthy population's cognitive functioning (Annex 7, Cognitive impairment map).

Justification

Interventions for rehabilitation of cognitive impairment aim to restore and/or compensate for cognitive impairment.

Restorative interventions may include education of the patient and caregiver on the condition in order to identify techniques to engage in desired tasks while managing symptoms, and cognitive exercises (e.g. task-specific training, drills, computerized training, cognitive/behavioural feedback, lexical retrieval, and caregiver-mediated exercises) *(454)(179)(180)(181)(183)(185)(187)*. Focus should be initially on engagement in basic tasks or activities and progressing as appropriate toward more cognitively demanding activities. There is currently no evidence to support one type of

cognitive exercise over the other in post COVID-19 condition. The interventions applied should directly address the symptoms of cognitive dysfunction identified by the patient or formal testing and will depend upon the setting of service delivery.

Compensatory interventions may include skills training on self-management strategies such as simplifying large tasks into smaller components, increasing self-awareness for fatigue, recognizing limits of ability, taking breaks during screen time or work tasks, activity and energy management or pacing, and techniques to manage environmental stimuli such as light and noise. Patients report that skills training on self-management is most useful for them.

The use of assistive technology may be addressed in the context of external cues for memory, such as checklists or a reminder function on mobile devices for breaks and medication. Problem-solving approaches to promote development of strategies to address real world challenges and environmental modifications to the home and/or workplace (e.g. maintaining a place for keys, reducing noise, appropriate lighting) can also be useful *(179)(180)(181)(185)(187)(189)*.

Currently, there is no evidence to support one intervention over the other in post COVID-19 condition.

The panel estimates that the expected outcomes for restorative and compensatory approaches include improvement of attention, memory and executive functioning, and increased ability to perform self-care activities (e.g. bathing, dressing, grooming), instrumental activities of daily living (e.g. answering the phone, home management) and participating in work or education (e.g. online meetings, in-person tasks). Harms and adverse events are unknown or understudied.

Topic 10 Fatigue

Fatigue or exhaustion in post COVID-19 condition presents as subjective reports of severely depleted systemic energy levels, not proportional to activities or exertion and not alleviated by usual rest or sleep. Fatigue negatively impacts physical and cognitive function, quality of life, social participation and employment *(388)(389)(412)(191)(193)(461)*.

Conditional recommendation for

For the clinical rehabilitation management of fatigue in adults with post COVID-19 condition we suggest using a combination of education, skills-training on energy conservation techniques such as pacing approaches and, in the absence of PESE, a cautious return to symptom-titrated physical exercise training. The provision and training in the use of assistive products and environmental modifications may be considered for people experiencing levels of fatigue that limit instrumental activities of daily living. Psychological support may be offered to support coping with the symptom *[Conditional recommendation]*.

Practical info

Patient-reported outcome measures of fatigue can be used to identify, assess, and measure change over time *(405)(462)(463)(464)*.

Symptom-titrated physical activity means engaging in physical activities, that may include exercise, only at a level guided by the presence and severity of symptoms, to mitigate exacerbating symptoms. Activities can be titrated up and down, depending on the episodic nature of symptoms experienced *(465)*.

Excluding PESE before commencing exercise therapy, and careful monitoring for PESE both during and after exercise, should be considered *(361)(382)(406)(195)*.

Physical exercise training should be adapted to the patient (e.g. pregnant women, older people).

Evidence to decision

Certainty of the evidence	No RCT or NRSI with comparator have been identified for the rehabilitation management of fatigue. Hence, no GRADE certainty of evidence assessment has been applied (Annex 6, Fatigue PCC interventions). The recommendation is based on expert evidence and evidence for the rehabilitation management of fatigue in other conditions. There is moderate certainty for the management of fatigue with exercise therapy in other long-term conditions *(466)(467)(468)*, however there is uncertainty how this evidence applies to people experiencing post-exertional symptom exacerbation *(469)(197)*.

Overall, certainty of evidence is low to moderate for educational interventions and low for fatigue self-management including pacing in other conditions *(197)* (Annex 7, Fatigue map).

Justification

Interventions for rehabilitation may include education about fatigue and its impact on physical, cognitive, emotional, and social energy demands *(412)(193)*, the importance of quality sleep and rest, and the often episodic and unpredictable nature of fatigue in post COVID-19 condition *(156)(158)*. Skills training on energy conservation techniques may include techniques for activity and energy management or pacing (including the provision of an assistive product to reduce the impact of fatigue), learning individual triggers and patterns to fatigue symptoms using activity and symptom diaries, strategies for prioritizing and planning including communication of health challenges and task delegation *(361)(382)(193)(199)*, and techniques for building quality rest into routines effectively *(411)(412)*. People living with post COVID-19 condition find advice on pacing their activities that is given as soon as possible and practical advice on how to modify some activities helpful.

In the absence of PESE *(361)(382)(406)(195)* a cautious return to symptom-titrated physical activity and/or exercise, may improve physical function and fatigue in people living with post COVID-19 condition *(444)(201)(470)(471)*.

Consider providing and training in the use of assistive products and environmental modifications at home or at work to assist with activity and energy management or pacing *(411)(412)(193)*, and to support mobility and activities of daily living *(150)(411)(400)* (see topic Return to everyday activities and work).

Consider discussing psychological support, including its principles, that it may help in managing symptoms such as fatigue, and could support distress associated with having an illness *(150)*. If the person with post COVID-19 condition would like to use psychological support, cognitive behavioural therapy (CBT) can be considered *(150)(472)*.

Currently, there is no evidence to support one intervention over the other in post COVID-19 condition.

Energy conservation techniques are considered safe *(361)(382)(410)(406)(411)(400)(415)*, and no evidence suggests risk of harm. No harm has been described in exercise intervention studies in post COVID-19 condition *(444)(445)(201)(470)(471)*, but there is the potential for harm by doing too much exertion too early, pushing through symptoms, and not using symptom-titrated physical activity *(388)(407)(408)(473)(474)*. CBT aims to support coping with fatigue and to improve functioning.

Topic 11 Mental health

People who experience depression following COVID-19 manifest core symptoms including persistent low mood and sadness, as well as markedly diminished interest in pleasurable activities for at least two weeks. Additional symptoms of depression include sleep disturbances, changes in appetite, fatigue, experiencing beliefs of worthlessness and considering self-harm or suicide. Patients with anxiety symptoms may appear restless, have uncontrollable or racing thoughts, concentration difficulties, feelings of dread and may also experience difficulties with sleep, appetite, and irritability.

Conditional recommendation for

For the clinical rehabilitation management of anxiety and depression in adults with post COVID-19 condition we suggest using psychological support and, in the absence of PESE, physical exercise training. In addition, mindfulness-based approaches and peer support groups may be useful to reduce distress in some people with post COVID-19 condition when managing long-term symptoms *[Conditional recommendation]*..

Practical info

Excluding PESE before commencing exercise therapy, and careful monitoring for PESE both during and after exercise, should be considered *(361)*.

Physical exercise training should be adapted to the patient (e.g. pregnant women, older people).

In addition, antidepressants (e.g. amitriptyline, fluoxetine) may be considered for depression in consultation with the person and considering personal preferences, age, concurrent medical conditions, mental health conditions (e.g. bipolar disorder) and side-effects *(475)(476)*.

Depressive symptoms can lead to reduced motivation and problem solving, thus impacting the ability for individuals to participate in the rehabilitation process. Perceived stigmatization regarding mental health treatment and disorders may further delay access to care for individuals with depression or anxiety symptoms. It is therefore important for general and more specialized health care and rehabilitation providers to be able to recognize signs of possible mental health conditions, to use effective communication skills and promote respect and dignity, and to be able to manage or refer persons presenting with mental health conditions *(475)*.

Evidence to decision

Certainty of the evidence

The certainty of direct evidence has been graded very low for respiratory muscle training compared to no intervention (Annex 6, Mental health PCC interventions). The interventions in the recommendation have been proposed considering evidence for interventions for rehabilitation of anxiety and depression in other health conditions (Annex 7)*(475)(477)* as well as expert evidence. The certainty of evidence is very low to moderate for physical exercise training in several conditions (Mental health map).

Justification

Psychological treatments including interpersonal therapy (IPT), CBT, and behaviour activation and problem-solving counselling, are recommended for the management of anxiety and depression *(478)(479)(475)(477)*. There is not enough evidence to support one psychological treatment over the other in post COVID-19 condition. However, online computerized CBT has shown to effectively reduce depression and anxiety compared with treatment as usual in patients with a history of COVID-19 *(480)(481)*.

Physical exercise training including aerobic exercises reduces depression and anxiety symptoms in patients with a respiratory condition *(487)* and patients with an immediate history of COVID-19 *(398)(435)(470)(482)*. A symptom-titrated exercise programme is recommended. Both structured *(398)(435)(470)(482)* and unstructured *(483)* exercise programmes have demonstrated subjective improvements in quality of life for participants.

Currently, there is no evidence to support one intervention over the other in post COVID-19 condition. However, CBT and a co-intervention such as aerobic exercise may reduce depressive symptoms more than aerobic exercise alone *(484)*.

Mindfulness-based approaches (e.g. mindfulness-based stress reduction) using a structured individual or group programme focusing on mindfulness meditation and stress reduction have demonstrated small improvements in anxiety, depression, and sleep in other chronic conditions *(485)*.

Patients report that peer group support is helpful; they find that acknowledgment of their distress is useful and helps to alleviate their distress. Many people turn to social media and support groups (online or face to face) for support and find them to be a valuable way to share experiences, knowledge and resources with others in a similar situation. For some, this communication has helped to validate patient experiences and provided reassurance they were not alone in their struggle with long-term symptoms *(486)*.

It is anticipated that individuals would demonstrate subjective and objective improvement in quality of life, depression symptoms, and anxiety symptoms following initiation of interventions such as physical exercise training and CBT. No adverse events were reported in the studies examined *(398)(435)(470)(478)(479)(480)(481)(485)(487)(482)(483)*.

Topic 12 Olfactory impairment

Post-viral olfactory dysfunction (PVOD) after SARS-CoV-2 infection is a cluster of impairments that persist after 4 weeks: loss of olfactory function (hyposmia or anosmia), or symptomatically altered function (parosmia, phantosmia and the recently described olfactory perseveration, or "smell lock") *(202)(204)*.

Conditional recommendation for

For the clinical rehabilitation management of olfactory impairment in adults with post COVID-19 condition we suggest using education and skills training for olfactory training *[Conditional recommendation]*.

Practical info

Although full assessment of olfactory function with smell testing is ideal, the subjective experience of smell loss should be enough to guide institution of this intervention for rehabilitation.

The commonest delivery mechanism for the odours is via essential oils in screw-cap jars. These are simple and easily available in many countries but may present a challenge in low-resource settings. In the absence of access to these specific odorants, other locally available odorants may be substituted, although there is no evidence to support this.

The information for olfactory training can be effectively delivered via the internet as well as other media.

Evidence to decision

Certainty of the evidence	No direct evidence based on effectiveness studies for rehabilitation of olfactory impairment in post COVID-19 condition is yet available (Annex 6). No GRADE certainty of evidence assessment has been applied. Olfactory training has been shown to be effective in other post-viral olfactory loss, which were known to be associated with other coronaviruses *(488)(205)*.

Justification

Olfactory training is the repeated, deliberate attempts at smelling a set of known odours, usually twice a day over at least 3 months *(488)(205)(207)*. The rehabilitation is self-delivered at home and requires no medical supervision or intervention. The available evidence is for training with the so-called "Hummel four" odorants (rose, clove, eucalyptus and lemon).

The expected outcome is that overall olfactory function, although variable, improves in most cases *(488)*. The panel estimates that harms are very unlikely.

Topic 13 Orthostatic intolerance

Orthostatic intolerance results from autonomic dysregulation and manifests in the form of blood pressure and heart rate variabilities with upright positions or standing, temperature dysregulation, excessive sweating, lightheadedness, chest pain and syncope *(489)(490)(491)(209)*.

Conditional recommendation for

For the clinical rehabilitation management of orthostatic intolerance in adults with post COVID-19 condition we suggest using a combination of education and skills training on self-management strategies and, in the absence of PESE, physical exercise training. Environmental modifications may be useful to support activities of daily living for people experiencing difficulties with upright positions or standing *[Conditional recommendation]*.

Practical info

Some people with PESE have chronotropic incompetence to the extent that it meets clinical criteria for orthostatic intolerance. Excluding PESE before commencing exercise therapy, and careful monitoring for PESE both during and after exercise, should be considered *(361)*.

Autonomic dysregulation can cause symptoms that overlap with orthostatic intolerance in the absence of orthostatic haemodynamic changes and it should be considered as a potential mechanism (e.g. fatigue and PESE secondary to autonomic dysfunction without signs of orthostatic intolerance).

Physical exercise training should be adapted to the patient (e.g. pregnant women, older people).

Evidence to decision

Certainty of the evidence	No direct evidence based on effectiveness studies for rehabilitation of orthostatic intolerance in post COVID-19 condition is yet available (Annex 6). No GRADE certainty of evidence assessment has been applied. Current level of evidence for efficacy of these interventions for orthostatic intolerance in

post COVID-19 condition is based on expert opinion. The recommendation is based on expert evidence.

Justification

Patient education and skills training for self-management should include the following: guidance on avoidance of symptom exacerbating factors such as warm environments, hot showers, straining, sudden moves from the supine or seated position to the upright position, and ingestion of large meals; simple isometric counterpressure manoeuvres such as tensing thighs, and folding arms and legs; fluid and salt repletion, and use of compression garments at lower limbs, waist and abdominal regions *(361)(490)(492)(211)(213)*. Physical activity might be encouraged to mitigate deconditioning, which may exacerbate orthostatic intolerance.

Physical exercise programmes have aerobic and resistance (e.g. isometric) elements. Training in non-upright positions such as recumbent bike exercises are recommended as orthostasis may be problematic *(490)(491)(215)*.

Environmental modifications should be considered to enhance safety and to avoid supine hypertension with activities of daily living *(491)*. Patients report improvement with advice on modifying activities with aids and adjustments to the upright position (e.g. the use of a perching or shower stool to enable sitting for usually upright tasks, or long handled equipment to reduce the need to bend down) (see topic Return to everyday activities and work).

Currently, there is no evidence to support one intervention over the other in post COVID-19 condition.

Interventions for rehabilitation aim to reduce the negative impact of orthostatic intolerance on functioning by reducing hypovolaemia, avoiding orthostatic hypotension and tachycardia *(361)(490)(491)(211)(213)*.

Topic 14 Swallowing impairment

Dysphagia in post COVID-19 condition is an acquired swallowing disorder that most likely results from weakness and inefficiency of the oral musculature and may have contributing symptoms of pain, exhaustion, and poor attention or memory. It most often presents with pharyngeal and laryngeal signs or symptoms, including delayed initiation of the swallow and coughing, choking, throat clearing, and voice changes (e.g. gurgly/wet voice) after the swallow. COVID-19-related dysphagia is mainly reported as post-extubation dysphagia *(493)(494)(495)(496)*. The existence of non-intubation dysphagia is also reported *(497)* but may not be as prevalent *(498)*.

Conditional recommendation for

For the clinical rehabilitation management of swallowing impairment in adults with post COVID-19 condition we suggest using a combination of education and skills training on positioning, manoeuvres and dietary modifications, and swallowing exercises *[Conditional recommendation]*.

Practical info

Identifying disordered swallowing physiology with instrumental evaluation (e.g. flexible endoscopic evaluation of swallowing [FEES] and videofluoroscopic swallowing study [VFSS]) will help to establish the intervention strategy, however, in low-resource settings where the instrumental evaluation may not be immediately accessible, the first step may be to apply common aspiration risk reduction strategies, including the use of positioning strategies and food/liquid modification with or without exercise training. Note that silent aspiration is not able to be reliably determined without instrumental evaluation and poses a threat for upper respiratory infection.

Interventions may be implemented in isolation or in combinations to control bolus flow and/or improve swallowing physiology.

Cognitive impairment (e.g., attention, memory) may impact the implementation of recommended interventions (see topic Cognitive impairment).

Diet texture and consistency modifications may follow a standardized scale *(217)(218)*.

Evidence to decision

Certainty of the evidence

There are no data from clinical trials addressing rehabilitation of dysphagia in post COVID-19 condition (Annex 6) and no GRADE certainty of evidence assessment has been applied. Large numbers of clinical studies and condition-specific systematic reviews within and across diverse patient populations support this recommendation. However, interventions for rehabilitation of dysphagia are not uniformly applied or standardized and only small-to-medium sized clinical studies support their use *(499)(500)(501)(502)* (Annex 7, Swallowing impairment map).

Justification

Education and skills training about positioning *(499)(503)(504)(505)(506)(507)(508)(509)(510)(511)*, manoeuvres *(499)(506)(512)(220)(222)(224)(226)* and diet texture and consistency modifications *(217)(218)(511)(228)(229)* aim to provide airway safety for oral intake.

Swallowing exercises target strengthening and coordination resulting in a more efficient system *(499)(500)(513)(514)(515)*.

Currently, there is no evidence to support one intervention over the other in post COVID-19 condition.

These interventions are applicable to all patients with dysphagia and anatomy that is not surgically altered. It is anticipated that interventions improve nutrition and hydration, avoid upper respiratory infection, and improve well-being *(516)*.

Topic 15 Voice impairment

Dysphonia in post COVID-19 condition is identified by a vocal quality which may be hoarse, rough, raspy, strained, weak, breathy, or gravely. It has been reported in COVID-19 patients who required supplemental oxygen (e.g. nasal canula, non-invasive ventilation, invasive ventilation) as well as in patients who did not require respiratory support *(517)(518)(231)(232)(234)(236)*.

Conditional recommendation for

For the clinical rehabilitation management of voice impairment in adults with post COVID-19 condition we suggest using education and skills training about voice rest and vocal behaviours. In addition, any combination of respiratory exercises and vocal training may be considered *[Conditional recommendation]*.

Practical info

It is advisable that assessments and outcome measures are used both to reflect the condition and progress of patients with dysphonia receiving rehabilitation *(519)(520)(521)(522)*.

Evidence to decision

Certainty of the evidence

There are no data from clinical trials addressing rehabilitation for dysphonia in post COVID-19 condition (Annex 6) or from Cochrane systematic reviews addressing rehabilitation of dysphonia in other health conditions (Annex 7). No GRADE certainty of evidence assessment has been applied. The interventions in the recommendation have been suggested based on large numbers of clinical studies among diverse patient populations receiving rehabilitation for dysphonia *(234)(238)(523)*.

Justification

Education and skills training regarding voice rest, hydration, and reducing laryngeal tension have been found to be effective in restoring normal phonation *(236)*.

Respiratory exercises are essential to restore adequate respiratory muscle function to support vocalization, vocal range, intonation, and to reduce vocal strain *(240)*.

Direct vocal training (e.g. Accent Method) and resonant vocal training may be helpful *(242)*.

Currently, there is no evidence to support one intervention over the other in post COVID-19 condition. There is, however, a lack of evidence for respiratory muscle and vocal cord dysfunction in people with post COVID-19 condition. Hence it is suggested to prioritize the provision of education and skills training regarding voice rest, hydration, and reducing laryngeal tension.

Not addressing dysphonia is associated with secondary harm of physical impairment (e.g. vocal nodule development) and reduction in work or education participation, and employment opportunities *(238)(243)*.

The expected outcomes from rehabilitation of COVID-19 related dysphonia include improvements in vocal stamina, voice quality, respiratory support for voicing, and well-being.

Topic 16 Return to everyday activities and work

In post COVID-19 condition, the combined effect of impairments in multiple body functions and structures typically manifests as difficulty with standing, mobility, stamina, and cognitive demands. These impact on the ability to carry out everyday activities, including leisure time and work *(524)(525)*. Optimizing independence in daily living and a return to work should be seen as goals of rehabilitation and health outcomes *(526)*. Limitations in ability to engage in activities of daily living and work can lead to long-term worklessness, which is significantly and independently associated with reduced life expectancy, quality of life, and income *(527)*.

Conditional recommendation for

Interventions for rehabilitation for a return to everyday activities in post COVID-19 condition could include education and skills training on energy conservation techniques, and the provision and training in the use of assistive products to those who need further assistance with activity management and mobility. For a return to work we suggest using a return to work action plan with a prolonged and flexible phased return. Environmental modifications at work may be needed based on an individualized workplace risk assessment of personal capabilities matched to work requirements *[Conditional recommendation]*.

Practical info

To inform an individual pacing approach, assessment of daily activities should take place in a real life context, where the burden of daily life and the impact of COVID-19 can be accurately estimated *(528)*. In identifying ‘readiness’ for work, ‘work-like activity’ (e.g. reading duration) can be compared with work requirements.

Workplace interventions principles can also be applied by line managers, human resources personnel or union representatives *(245)*.

Interventions in the recommendations can be applied across high- and low-resource settings as they are typically of low financial cost. Assistive product provision and environmental adaptations should consider the use of local resources in low-resource settings.

Work may aggravate new impairments e.g. heat may worsen autonomic dysfunction and new lung disease may increase vulnerability to some occupational diseases. Strenuous workplace exertion should be avoided until cardiorespiratory symptoms have settled *(529)(530)*. This may pose difficulty for people relying on strenuous or insecure employment.

Evidence to decision

Certainty of the evidence	There is no direct evidence based on intervention studies for return to everyday activities and work rehabilitation in post COVID-19 condition. No GRADE certainty of evidence assessment has been applied. The stated recommendation is based on a combination of expert evidence and evidence applied from comparable health conditions and disease processes *(531)*.

Justification

To enable participation in daily activities, education and skills training on energy conservation techniques, including activity and energy management or pacing, is suggested *(387)(532)(533)*. Persons are taught to apply a combination of self-monitoring, task assessment, planned activity, and rest. In post COVID-19 condition, it has been consistently observed that too-early return

to activities leads to symptom exacerbation or relapse, loss of confidence, and work loss. People with post COVID-19 condition need to be able to self-manage their energy at home before they start to work.

Consider providing and training in the use of assistive products (e.g. wheelchair, shower seat) and environmental modifications at home (e.g. perching stool or long handled equipment), to assist with activity and energy management or pacing *(411)(412)(193)*, support mobility and activities of daily living, and maintain or improve functional independence and quality of life *(150)(400)*. Additional environmental modifications should be considered for people with orthostatic intolerance such as handrails to prevent falls and enhance safety and head of the bed elevation of 10–20 degrees to avoid supine hypertension *(491)*. For people with cognitive impairment environmental modifications such as maintaining a place for keys, reducing noise, and appropriate lighting may be useful.

Environmental modifications at work should address the environment, timing and duration, responsibilities, and tasks. Modifications require individualized assessment of personal capabilities matched to work requirements *(529)*.

Workplace interventions include a return to work action plan with prolonged and flexible phased return, and an individualized workplace risk assessment. The return to work action plan *(534)(535)* between line manager and worker, and prolonged phased return (regularly reviewed, individualized, and flexible) are the essential components of a sustainable return to work with post COVID-19 condition *(245)*. For people with post COVID-19 condition experiencing PESE this may involve pacing in the workplace.

People with post COVID-19 condition may have neurocognitive impairment, which can lead to safety issues in the workplace and require a risk assessment. Some work situations may cause harm in the presence of cardiorespiratory symptoms *(530)(536)*.

The panel estimates there is a potential harm from not applying the suggested interventions for return to everyday activities and work in post COVID-19 condition, as a limited ability to engage in one's desired activities can negatively impact mental health, causing a cyclical and cascade effect of further negative outcomes.

Currently, there is no evidence to support one intervention over the other for a return to everyday activities and work in post COVID-19 condition.

Suggested workplace interventions have been shown to be effective in many chronic illnesses *(536)*.

3.13 Clinical research

A living mapping and systematic review of COVID-19 therapeutic studies is available *(249)*.

We recommend to collect standardized clinical data on all hospitalized patients to improve understanding of the natural history of the disease and contribute data to the WHO Global COVID-19 Clinical Data Platform (see website for details) *[Non-GRADE based recommendation]***.**

Remarks:

1. Member States are invited to contribute anonymized clinical data to the WHO Global COVID-19 Clinical Data Platform; contact: global_clinical_platform@who.int to get log-in credentials. This will serve to inform the public health and clinical response.
2. Four case record forms (CRFs) are now available: These can be accessed on the WHO website (251).
- *Core CRF;*
- *Pregnancy CRF;*
- *Multisystem inflammatory syndrome temporally associated with COVID-19 CRF;*
- *Post COVID-19 condition CRF.*

3. Clinical characterization research protocols are also available (540).

ACKNOWLEDGEMENTS

Funding

UNITAID, University of British Columbia.

Acknowledgements for antimicrobial resistance (AMR) and guideline pruning June 2024

WHO Steering Committee members: Janet V Diaz (Lead, Clinical Management Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Lisa Askie (Quality Assurance of Norms and Standards Department, Science Division, WHO Geneva, Switzerland); Silvia Bertagnolio (Communicable and Noncommunicable Diseases Division/Clinical Management Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Mercedes Bonet Semenas (Reproductive Health and Research Department, WHO Geneva, Switzerland); Jane A Cunningham (Emerging Diseases & Zoonoses, WHO Geneva, Switzerland); Wouter De Groote (Rehabilitation programme, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Tarun Dua (Mental Health and Substance Abuse Department, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Dennis Falzon (Global TB Programme, WHO Geneva, Switzerland); Fahmy Hanna (Mental Health and Substance Abuse Department, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Chiori Kodama (WHO Regional Office for the Eastern Mediterranean, Health Emergencies Programme); Tamano Matsui (WHO Regional Office for the Western Pacific/Health Emergencies Programme); Dina Pfeifer (WHO Regional Office for Europe, Health Emergencies Programme); Kamara Rashidatu Fouad (WHO Regional Office for Africa, Health Emergencies Programme); Andreas Alois Reis (Health Ethics & Governance Department, WHO Geneva, Switzerland); Jamie Rylance (Clinical Management Team for COVID-19 Response, Health Emergencies Programme); Nicoline Schiess (Mental Health and Substance Abuse Department, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Anthony Solomon (Control of Neglected Tropical Diseases Department, WHO Geneva, Switzerland); Yuka Sumi (Maternal, Newborn, Child and Adolescent Health and Ageing, Department of Life Course, WHO Geneva, Switzerland); Alejandra Velez (Clinical Management Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Andrea Vicari (Evidence and Intelligence for Action in Health Department, Incident Management Systems for COVID-19, Pan American Health Organization); Wilson Were (Maternal, Newborn, Child and Adolescent Health Department, Health Emergencies Programme, WHO Geneva, Switzerland); Pushpa Wijesinghe (WHO Regional Office for South-East Asia, Health Emergencies Programme).

Project officer: Julie Viry (Health Emergencies Programme, WHO Geneva, Switzerland).

Guideline Development Group (GDG) for AMR and guideline pruning recommendations:

Andre Ricardo Araujo Da Silva (Departamento de Materno Infantil, Universidade Federal Fluminense, Brazil); Heike Geduld (Emergency Medicine, Stellenbosch University, South Africa); David Hui (Stanley Ho Centre for Emerging Infectious Diseases, Chinese University of Hong Kong, Hong Kong SAR, China); Mohamed Ismail (Indira Gandhi Memorial Hospital, Maldives);Fabian Alberto Jaimes Barragan (Antioquia University Medellin, Colombia); Niranjan Kissoon (Department of Pediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Sanjeev Krishna (St George's University of London, United Kingdom); Yee-Sin Leo (National Centre for Infectious Diseases, Singapore); Thiago Lisboa (Coraçao Hospital, Sao Paulo, Brazil);Hela Manai (Emergency Medical Service Tunis, Tunisia);Emmanuel Nsutebu (Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates); Natalia Pshenichnaya (Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russian Federation);Nida Qadir (Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California, Los Angeles, United States); Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China);Shalini Sri Ranganathan (University of Colombo, Sri Lanka);Miriam Stegemann (Charité - Universitätsmedizin Berlin, Germany);Timothy Uyeki (Influenza Centers for Disease Control and Prevention, Atlanta, Georgia, United States);Evangelina Vazquez Curiel (community representative, Mexico), Sridhar Venkatapuram (King's College London, United Kingdom).

Methodologist: Gordon Guyatt (McMaster University, Canada).

Clinical Chairs: Neill Adhikari (Sunnybrook Health Sciences Centre and University of Toronto, Canada); Srinivas Murthy (Associate Professor, University of British Columbia, Canada).

Special thanks to the following collaborators for providing systematic reviews for AMR: Daniele Dona (Department of Women's and Children's Health, University of Padua, Italy).

Special thanks to the external reviewers for their insights on the recommendations on AMR and guideline pruning: Richard Kojan (Alliance for International Medical Action, Democratic Republic of the Congo).

Acknowledgements for awake prone positioning August 2023

WHO Steering Committee members: Janet V Diaz (Lead, Clinical Management Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); John Adabie Appiah (Clinical Management Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Lisa Askie (Quality Assurance of Norms and Standards Department, Science Division, WHO Geneva, Switzerland); Silvia Bertagnolio (Communicable and Noncommunicable Diseases Division/Clinical Management Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Mercedes Bonet (Reproductive Health and Research Department, WHO Geneva, Switzerland); Jane A Cunningham (Emerging Diseases & Zoonoses, WHO Geneva, Switzerland); Wouter De Groote (Rehabilitation programme, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Tarun Dua (Mental Health and Substance Abuse Department, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Dennis Falzon (Global TB Programme, WHO Geneva, Switzerland); Fahmy Hanna (Mental Health and Substance Abuse Department, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Rok Ho Kim (Quality Assurance of Norms and Standards Department, Science Division, WHO Geneva, Switzerland); Chiori Kodama (WHO Regional Office for the Eastern Mediterranean, Health Emergencies Programme); Takeshi Nishijima (WHO Regional Office for the Western Pacific/ Health Emergencies Programme); Mark Perkins (Department of Global Infectious Hazard Preparedness, Health Emergencies Programme, WHO Geneva, Switzerland); Dina Pfeifer (WHO Regional Office for Europe, Health Emergencies Programme); Kamara Rashidatu Fouad (WHO Regional Office for Africa, Health Emergencies Programme); Andreas Alois Reis (Health Ethics & Governance Department, WHO Geneva, Switzerland); Pryanka Relan (Integrated Health Services Department, Health Emergencies Programme, WHO Geneva, Switzerland); Ludovic Reveiz (Evidence and Intelligence for Action in Health Department, Incident Management Systems for COVID-19, Pan American Health Organization); Jamie Rylance (Clinical Management Team for COVID-19 Response, Health Emergencies Programme); Nicoline Schiess (Mental Health and Substance Abuse Department, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Anthony Solomon (Control of Neglected Tropical Diseases Department, WHO Geneva, Switzerland); Yuka Sumi (Maternal, Newborn, Child and Adolescent Health and Ageing, Department of Life Course, WHO Geneva, Switzerland); Alejandra Velez (Clinical Management Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Wilson Were (Maternal, Newborn, Child and Adolescent Health Department, Health Emergencies Programme, WHO Geneva, Switzerland); Pushpa Wijesinghe (WHO Regional Office for South-East Asia, Health Emergencies Programme).

Project officer: Julie Viry (Health Emergencies Programme, WHO Geneva, Switzerland).

Guideline Development Group (GDG) for awake prone positioning recommendation:

Ahmed Alhadyan (community representative, Saudi Arabia); Muna Al-Maslamani (Communicable Disease Center, Qatar); Andre Ricardo Araujo Da Silva (Departamento de Materno Infantil, Universidade Federal Fluminense, Brazil); Julie Benbenishty (Hadassah Hebrew University Hadassah Medical Organization, Israel); Maurizio Cecconi (Humanitas Research Hospital Milan, Italy); Binila Chacko (Division of Critical Care Medicine at Christian Medical College, Vellore, India); Malachy Clanchy (University of Pennsylvania, United States); Quoc Vu Dat (Department of Infectious Diseases, Hanoi Medical University, Hanoi, Viet Nam); Niamh Flynn (University College London Hospitals, United Kingdom); Nerina Harley (Royal Melbourne Hospital, Australia); Fabian Alberto Jaimes Barragan (Antioquia University Medellin, Colombia); Niranjan Kissoon (Department of Pediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Natalia Pshenichnaya (Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russian Federation); Louise Rose (King's College London, United Kingdom); Halima Salisu-Kabara (Sepsis Research Group, Nigeria); Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China); Tshokey Tshokey (JDW National Referral Hospital, Bhutan); Evangelina Vazquez Curiel (community representative, Mexico), Kathleen Vollman (Advancing Nursing LCC, United States).

Methodologist: Gordon Guyatt (McMaster University, Canada).

Clinical Chairs: Neill Adhikari (Sunnybrook Health Sciences Centre and University of Toronto, Canada); Srinivas Murthy (Associate Professor, University of British Columbia, Canada).

Special thanks to the following collaborators for providing systematic reviews for awake prone positioning: Ken Parhahar and Jason Weatherald (Critical Care Medicine, University of Calgary and Alberta Health Services, United States).

Special thanks to the external reviewers for their insights on the recommendations on awake prone positioning: Yaseen Arabi (King Saud bin Abdulaziz University for Health Sciences, Saudi Arabia); Richard Kojan (Alliance for International Medical Action, Democratic Republic of the Congo).

Acknowledgements for Infectious period and de-isolation November 2022

WHO Steering Committee members: Janet V Diaz (Lead, Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Benedetta Allegranzi (Infection Prevention and Control, Health Emergencies Programme, WHO Geneva, Switzerland); Lisa Askie (Quality Assurance of Norms and Standards Department, Science Division, WHO Geneva, Switzerland); April Baller (Infection Prevention and Control, Health Emergencies Programme, WHO Geneva, Switzerland); Silvia Bertagnolio (Communicable

and Noncommunicable Diseases Division/ Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Mercedes Bonet (Department of Reproductive Health and Research, WHO Geneva, Switzerland); Hannah Hamilton (Infection Prevention and Control, Health Emergencies Programme, Switzerland); John Adabie Appiah (Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Matthias Bonk (WHO Regional Office for Europe/Health Emergencies Programme); Vanessa Cramond (Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Tarun Dua (Department of Mental Health and Substance Abuse, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Kathleen Ann Dunn (Infection Prevention and Control, Health Emergencies Programme, WHO Geneva, Switzerland); Dennis Falzon (Global TB Programme, WHO Geneva, Switzerland); Fahmy Hanna (Department of Mental Health and Substance Abuse, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Rok Ho Kim (Quality Assurance of Norms and Standards Department, Science Division, WHO Geneva, Switzerland); Chiori Kodama (WHO Regional Office for the Eastern Mediterranean, Egypt); Krutika Kuppalli (Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Takeshi Nishijima (WHO Regional Office for the Western Pacific/Health Emergencies Programme, Philippines); Mark Perkins (Department of Global Infectious Hazard Preparedness, Health Emergencies Programme, WHO Geneva, Switzerland); Dina Pfeifer (WHO Regional Office for Europe/Health Emergencies Programme); Kamara Rashidatu Fouad (WHO Regional Office for Africa/ Health Emergencies Programme, Democratic Republic of the Congo); Pryanka Relan (Integrated Health Services Department/Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Ludovic Reveiz (Evidence and Intelligence for Action in Health Department, Incident Management Systems for COVID-19, Pan American Health Organization, United States); Julian Sacks (Department of Global Infectious Hazard Preparedness, Health Emergencies Programme, WHO Geneva, Switzerland); Nicoline Schiess (Department of Mental Health and Substance Abuse, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Alice Simniceanu (Infection Prevention and Control, Health Emergencies Programme, WHO Geneva, Switzerland), Yuka Sumi (Maternal, Newborn, Child and Adolescent Health and Ageing, Department of Life Course, WHO Geneva, Switzerland); Alejandra Velez (Clinical Team for COVID-19 Response, Health Emergencies Programme, Switzerland Geneva); Wouter De Groote (Rehabilitation Programme, Department of Noncommunicable Diseases, WHO Geneva, Switzerland); Wilson Were (Department of Maternal, Newborn, Child and Adolescent Health, Health Emergencies Programme, WHO Geneva, Switzerland); Pushpa Wijesinghe (WHO Regional Office for South-East Asia/Health Emergencies Programme, India).

Supporting project officer: Julie Viry (Health Emergencies Programme, WHO Geneva, Switzerland).

The WHO Steering Committee is fully responsible for decisions about guidance production and convening the GDG.

Guideline Development Group (GDG) for *Infectious period and de-isolation* recommendations:

Duncan Chanda (Institute for Medical Research and Training, Zambia); John Conly (University of Calgary and Alberta Health Services, Canada); Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Hanoi, Viet Nam); Madiha Hashmi (Ziauddin University, Karachi, Pakistan); Beverley Hunt (King's College, London, United Kingdom); Fabian Alberto Jaimes Barragan (Antioquia University Medellín, Colombia); Kushlani Jayatilleke (Sri Jayewardenepura General Hospital, Sri Lanka); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi, India); Niranjan Kissoon (Department of Pediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Anna Levin (University of São Paulo, Brazil); Moi Lin Ling (Singapore General Hospital, Singapore); Rakesh Lodha (Department of Pediatrics, All India Institute of Medical Sciences, India); Hela Manai (Emergency Medical Service Tunis, Tunisia); Shaheen Mehtar (Infection Control Africa Network, South Africa); Nida Qadir (Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California, Los Angeles, United States); Emmanuel Nsutebu (Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates); Tochi Okwor (Centre for Disease Control and Prevention, Nigeria); Diamantis Plachouras (European Centre for Disease Prevention and Control, Sweden); Manu Shankar-Hari (King’s College London, United Kingdom); Shalini Sri Ranganathan (University of Colombo, Sri Lanka); Paul Tambyah (National University of Singapore, Singapore); Sridhar Venkatapuram (King’s College London, United Kingdom).

Methodologist: Gordon Guyatt (McMaster University, Canada).

Clinical Chairs: Neill Adhikari (Sunnybrook Health Sciences Centre and University of Toronto, Canada); Srinivas Murthy (Associate Professor, University of British Columbia, Canada).

Special thanks to the following collaborators for providing systematic reviews for infectious period: Qiukui Hao (McMaster University, Canada); Ya Gao (McMaster University, Canada).

Special thanks to the external reviewers for their insights on the recommendations on infectious period: Aula Abbara (Operational Center Amsterdam, Médecins Sans Frontières, Netherlands); Yaseen Arabi (King Saud bin Abdulaziz University for Health Sciences, Saudi Arabia); Kerry Dierberg (Médecins Sans Frontières, United States); Marcio da Fonseca (Access Campaign, Médecins Sans Frontières, Netherlands); Richard Kojan (Alliance for International Medical Action, Democratic Republic of the Congo); Carolina Nanclares (Médecins Sans Frontières, Argentina); Saschveen Singh (Médecins Sans Frontières, Australia); Armand Sprecher (Médecins Sans Frontières, Belgium).

Acknowledgements for *Rehabilitation of adults with post COVID-19 condition* September 2022

WHO Steering Committee members: Janet V Diaz (Lead, Clinical Team for COVID-19 Response, Health Emergency Programme, WHO Geneva, Switzerland); Alarcos Cieza (Sensory Functions, Disability and Rehabilitation, Department of Noncommunicable Diseases, WHO Geneva, Switzerland); Wouter De Groote (Technical Advisor, Rehabilitation Programme, Department of Noncommunicable Diseases, WHO Geneva, Switzerland); Kamaraj Devapitchai (Disability and Rehabilitation, Department of Noncommunicable Diseases, WHO Geneva, Switzerland); Tarun Dua (Department of Mental Health and Substance Abuse, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Fahmy Hanna (Department of Mental Health and Substance Abuse, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Krutika Kuppalli (Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Nicoline Schiess (Department of Mental Health and Substance Abuse, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland).

WHO convened GDG panel members (F/M 12/11): Martin B Brodsky (Johns Hopkins University, United States); Darren Brown (Chelsea and Westminster Hospital NHS Foundation Trust, United Kingdom); Malachy J Clancy (Good Shepherd Penn Partners, United States); Edith Cup (Radboud University Medical Center, Nijmegen, Netherlands); Simon Décary (University of Sherbrooke, Canada); Pamela Enderby (International Association of Communication Sciences and Disorders, United Kingdom); Simon B C Gane (University College London, United Kingdom); Alla Guekht (Moscow Research and Clinical Center for Neuropsychiatry, Russian Federation); Brian J Hall (New York University Shanghai, China); Arifa Jahan Ema (Bangladesh Health Professions Institute, Bangladesh); Carlotte Kiekens (Chair, IRCCS MultiMedica, Milan, Italy); Rebecca Livingston (University College London Hospitals, United Kingdom); Amina Muazzam (Lahore College for Women University, Pakistan); Masahiko Mukaino (School of Medicine, Fujita Health University, Japan); Deshini Naidoo (University of KwaZulu-Natal, South Africa); Alice Namanja (Kamuzu University of Health Sciences, Malawi); Babatunde G Ogundunmade (Jos University Teaching Hospital, Nigeria); Clare R Rayner (Society of Occupational Medicine, United Kingdom); Sally Singh (University of Leicester, United Kingdom); Antoni Siso-Almirall (University of Barcelona, Spain); Laura Tabacof (Icahn School of Medicine at Mount Sinai, United States); Simon Wessely (King's College London, United Kingdom); Wenguang Xia (Hubei Rehabilitation Hospital, China).

Methodologist: Lisa Askie (Quality Assurance of Norms and Standards Department, Science Division, WHO Geneva, Switzerland).

Special thanks to Cochrane Rehabilitation for providing evidence synthesis and systematic review: Chiara Arienti (IRCCS Fondazione Don Gnocchi, Milan, Italy); Paolo Boldrini (Italian Society of Physical and Rehabilitation Medicine); Simon Décary (University of Sherbrooke, Canada); Stefano Giuseppe Lazzarini (IRCCS Fondazione Don Gnocchi, Milan, Italy); Stefano Negrini (University "La Statale", Milan, Italy).

Special thanks to the internal and external reviewers for their insights: Mercedes Bonet-Semanas (Sexual and Reproductive Health, WHO Geneva, Switzerland); François Boyer (Reims Champagne Ardenne University, France); Matteo Cesari (Maternal, Newborn, Child, and Adolescent Health and Ageing, Health Emergencies Programme, WHO Geneva, Switzerland); Todd Davenport (University of the Pacific, United States); Brandon Gray (Department of Mental Health and Substance Abuse, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Susanne Nielsen (Health Workforce and Service Delivery Unit, WHO Regional Office for Europe); Ana María Posada (Universidad de Antioquia, Colombia); Ludovic Reveiz (Evidence and Intelligence for Action in Health Department, Incident Management Systems for COVID-19, Health Emergencies Programme, Pan American Health Organization, United States); Rachel Tarrant (Leeds Community Healthcare NHS Trust, United Kingdom); Valiyaparambath Purushothaman Vandana (National Institute of Mental Health and Neurosciences, Bangalore, India); Tracy Vannorsdall (Johns Hopkins University, United States); Stephanie Verheyden (patient, Belgium); Inka Weissbecker (Department of Mental Health and Substance Abuse, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland).

Acknowledgements for *Clinical management of COVID-19: living guideline* June 2022

WHO Steering Committee members: Janet V Diaz (Lead, Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Lisa Askie (Quality Assurance of Norms and Standards Department, Science Division, WHO Geneva, Switzerland); April Baller (Infection Prevention and Control, Health Emergencies Programme, WHO Geneva, Switzerland); Silvia Bertagnolio (Communicable and Noncommunicable Diseases Division/Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Mercedes Bonet (Department of Reproductive Health and Research, WHO Geneva, Switzerland); Hannah Hamilton (Infection Prevention and Control, Health Emergencies Programme, WHO Geneva, Switzerland); Vanessa Cramond (Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Wouter De Groote (Rehabilitation Programme, Department of Noncommunicable Diseases, WHO Geneva, Switzerland); Tarun Dua (Department of Mental Health and Substance Abuse, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Kathleen Ann Dunn (Infection Prevention and Control, Health Emergencies Programme, WHO Geneva, Switzerland); Dennis Falzon (Global TB Programme, WHO Geneva, Switzerland); Fahmy Hanna (Department of Mental Health and Substance Abuse, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Rok Ho Kim (Quality Assurance of Norms and Standards Department, Science Division, WHO Geneva, Switzerland); Chiori Kodama (WHO Regional Office for the Eastern Mediterranean, Egypt); Krutika

Kuppalli (Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Marta Lado (Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Mark Perkins (Department of Global Infectious Hazard Preparedness, Health Emergencies Programme, WHO Geneva, Switzerland); Dina Pfeifer (WHO Regional Office for Europe/Health Emergencies Programme); Pryanka Relan (Integrated Health Services Department/Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Ludovic Reveiz (Evidence and Intelligence for Action in Health Department, Incident Management Systems for COVID-19, Pan American Health Organization, United States); Julian Sacks (Department of Global Infectious Hazard Preparedness, Health Emergencies Programme, WHO Geneva, Switzerland); Nicoline Schiess (Department of Mental Health and Substance Abuse, Communicable and Noncommunicable Diseases Division, WHO Geneva, Switzerland); Yuka Sumi (Maternal, Newborn, Child and Adolescent Health and Ageing, Health Emergencies Programme, WHO Geneva, Switzerland); Bharath Kumar Tirupakuzhi Vijayaraghavan (Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Alejandra Velez (Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Wilson Were (Department of Maternal, Newborn, Child and Adolescent Health and Ageing, Health Emergencies Programme, WHO Geneva, Switzerland).

Supporting project officers: Anouar Bouraoui (Health Emergencies Programme, Health Care Readiness Unit, WHO Geneva, Switzerland); Anne Colin (Health Emergencies Programme, WHO Geneva, Switzerland); Julie Viry (Health Emergencies Programme, WHO Geneva, Switzerland).

The WHO Steering Committee is fully responsible for decisions about guidance production and convening the GDG.

Guideline Development Group (GDG) for advanced respiratory support recommendations: Wagdy Amin (Ministry of Health and Population, Egypt); Andre Ricardo Araujo da Silva (Federal Fluminense University, Niterói, Brazil); Diptesh Aryal (Mediciti Hospital, Nepal); Carolyn S Calfee (University of California, San Francisco, United States); Maurizio Cecconi (Humanitas Research Hospital Milan, Italy); Binila Chacko (Division of Critical Care Medicine, Christian Medical College, Vellore, India); Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Hanoi, Viet Nam); Rob Fowler (Sunnybrook Health Sciences Centre, Toronto, Canada); Heike Geduld (Emergency Medicine, Stellenbosch University, South Africa); Patrick Gee (patient panel member, Virginia, United States); Madiha Hashmi (Ziauddin University, Karachi, Pakistan); Manai Hela (Emergency Medical Service Tunis, Tunisia); David Hui (Department of Medicine and Therapeutics, Stanley Ho Centre for Emerging Infectious Diseases, Chinese University of Hong Kong, Hong Kong SAR, China); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi, India); Niranjan Kissoon (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Arthur Kwizera (Makerere College of Health Sciences, Kampala, Uganda); Yee-Sin Leo (National Centre for Infectious Diseases, Singapore); Thiago Lisboa (Coraçao Hospital, São Paulo, Brazil); Louise Thwaites (Centre for Tropical Medicine and Global Health, University of Oxford; Ho Chi Minh City, Viet Nam); Swagata Tripathy (All India Institute of Medical Sciences, Bhubaneswar, India).

Methodologist: Gordon Guyatt (McMaster University, Canada).

Clinical Chairs: Neill Adhikari (Sunnybrook Health Sciences Centre and University of Toronto); Srinivas Murthy (Associate Professor, University of British Columbia, Vancouver, Canada).

We would like to acknowledge the Guidance Support Collaboration Committee which provided the coordination to allow the rapid development of the advanced respiratory support recommendations: Neill Adhikari (Sunnybrook Health Sciences Centre and University of Toronto); Lisa Askie (Quality Assurance of Norms and Standards Department, Science Division, WHO Geneva, Switzerland); Janet V Diaz (Lead, Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Guyatt (McMaster University, Canada); Marta Lado (Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland); Mark Srinivas Murthy (University of British Columbia, Canada); Bharath Kumar Tirupakuzhi Vijayaraghavan (Clinical Team for COVID-19 Response, Health Emergencies Programme, WHO Geneva, Switzerland).

Special thanks to the following collaborators for providing systematic reviews for advanced respiratory support: Shannon Kelly (University of Ottawa Heart Institute, Canada); Georges Wells (University of Ottawa Heart Institute, Canada).

Special thanks to the external reviewers for their insights on the recommendations on advanced respiratory support: Aula Abbara (Manson Unit, Médecins Sans Frontières, United Kingdom); Gabriel Alcoba (Médecins Sans Frontières, Switzerland); Yaseen Arabi (King Saud bin Abdulaziz University for Health Sciences, Saudi Arabia); Francisco Bartolome (Health Ministry/Médecins Sans Frontières, Spain); Marcio da Fonseca (Médecins Sans Frontières, Netherlands); Richard Kojan (Alliance for International Medical Action and Teaching Hospital of Kinshasa, Democratic Republic of the Congo); Bhargavi Rao (London School of Hygiene and Tropical Medicine/ Médecins Sans Frontières, United Kingdom); Saschveen Singh (Médecins Sans Frontières, Australia); Armand Sprecher (Médecins Sans Frontières, Belgium).

Special thanks to the MAGIC Evidence Ecosystem Foundation for their support in the publication process through MAGICapp: Per Olav Vandvik, Arnav Agarwal, Lyubov Lytvyn, Stijn Rita Patrick van de Velde, Ying Wang, Linan Zeng, Dena Zeraatkar.

Acknowledgements for *Clinical management of COVID-19: living guideline* January 2022

Special thanks to the Guideline Development Group (GDG) for MISC-C recommendations: Duncan Chanda (Adult Infectious Disease Centre, University Teaching Hospital, Lusaka, Zambia); Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Hanoi, Viet Nam); Gabina Del Olmo Gonzalez (parent of patient, Italy); Ann De Sutter (University of Gent, Belgium); Bin Du (Peking Union Medical College Hospital, China); Stephen Freedman (Alberta Children's Hospital Research Institute, University of Calgary, Canada); Heike Geduld (Emergency Medicine, Stellenbosch University, South Africa); Madiha Hashmi (Ziauddin University, Karachi, Pakistan); Manai Hela (Emergency Medical Service Tunis, Tunisia); Beverley Hunt (Thrombosis and Haemostasis, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom); Fyezah Jehan (Aga Khan University Hospital, Karachi, Pakistan); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi, India); Yae-Jean Kim (Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea); Niranjan Kissoon (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Yee-Sin Leo (National Centre for Infectious Diseases, Singapore); Rakesh Lodha (Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India); Greta Mino (Alcivar Hospital in Guayaquil, Ecuador); Emmanuel Nsutebu (Sheikh Shakhbout Medical City, Abu Dhabi); Pablo Rojo (Pediatric Infectious Diseases Unit, Hospital 12 de Octubre, Madrid, Spain); Manu Shankar-Hari (University College London, London, United Kingdom); Shalini Sri Ranganathan (University of Colombo, Sri Lanka); Sridhar Venkatapuram (King's College, London); Monica Garrido Zamora (parent of patient, Italy).

Special thanks to the following collaborators for providing systematic reviews for MIS-C:
Mirjam Kool (Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, United Kingdom); James Martin (Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, United Kingdom); Harsita Patel (Paediatric Infectious Diseases, Imperial College London); Barney Scholefield (Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, University of Birmingham, Paediatric Intensive Care Unit, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, United Kingdom); Elizabeth Whittaker (Paediatric Infectious Diseases, Imperial College London).

We would like to acknowledge the **Guidance Support Collaboration Committee** which provided the coordination to allow the rapid development of the MISC recommendations: Neill Adhikari (Sunnybrook Health Sciences Centre and University of Toronto); Lisa Askie (WHO); Rajiv Bahl (WHO); Janet V Diaz (WHO); Karen Edmond (WHO); Gordon Guyatt (McMaster University, Canada); Marta Lado (WHO); Srinivas Murthy (University of British Columbia, Canada); Jacobus Preller (WHO); Archana Seahwag (WHO); Wilson Were (WHO).

Special thanks to the external reviewers for their insights on the recommendations on MISC-C: Richard Kojan (ALIMA and Teaching Hospital of Kinshasa, Democratic Republic of the Congo); Gabriel Alcoba, Francisco Bartolome, Marcio da Fonseca, Bhargavi Rao, Saschveen Singh, Armand Sprecher (Médecins Sans Frontières).

Acknowledgements for *Clinical management of COVID-19: interim guidance* 18 January 2021

WHO Steering Committee members: Janet V Diaz (Lead, Clinical Team for COVID-19 Response, Health Emergencies Programme, Geneva); John Appiah (Lead, case management, WHO Regional Office for Africa); Lisa Askie (Quality Assurance of Norms and Standards Department); April Baller (Infection Prevention and Control); Anshu Banerjee (Department of Maternal, Newborn, Child and Adolescent Health and Ageing); Silvia Bertagnolio (Communicable and Noncommunicable Diseases Division/Clinical Team for COVID-19 Response); Mercedes Bonet (Department of Reproductive Health and Research); Andrea Bosman (Global Malaria Programme); Marie-Charlotte Bousseau (Palliative Care); Maurice Bucagu (Department of Sexual and Reproductive Health and Research); Neerja Chowdhary (Department of Mental Health); Jane Cunningham (Global Malaria Programme); Meg Doherty (Treatment and Care, Department of HIV/AIDS); Tarun Dua (Programme for Neurological Diseases and Neuroscience, Management of Mental and Brain Disorders in the Department of Mental Health and Substance Abuse); Nedret Emiroglu (Country Readiness Strengthening, Health Emergencies Department); Dennis Falzon (Global TB Programme); Nathan Ford (Department of HIV/AIDS and Global Hepatitis Programme); Licé Gonzalez Angulo (Global TB Programme); John Grove (Quality Assurance of Norms and Standards Department); Laurence Grummer-Strawn (Department of Nutrition for Health and Development); Fahmy Hanna (Department of Mental Health and Substance Abuse); Peter Hughes (Department of Mental Health and Substance Abuse); Benedikt Huttner (Infection Control Programme and Division of Infectious Diseases); Ernesto Jaramillo (Global TB Programme); Maria Van Kerkhove (Health Emergencies Programme); Caron Kim (Sexual and Reproductive Health and Research); Rok Ho Kim (Quality Assurance of Norms and Standards Department); Kavitha Kolappa (Department of Mental Health and Substance Abuse); Teresa Kortz (WHO); Gary Kuniyoshi (WHO Regional Office for the Western Pacific/Health Emergencies Programme); Ornella Lincetto (WHO Representative of Bhutan); Wouter De Groote (Rehabilitation Programme, Department of Noncommunicable Diseases); Lorenzo Moja (Health Products Policy and Standards Department); Susan Norris (Health Metrics and Measurement); Olufemi Oladapo (Sexual and Reproductive Health and Research Department); Peter Olumese (Global Malaria Programme); Mark van Ommeren (Department of Mental Health and Substance Abuse); Martina Penazzato (Paediatric Lead for HIV, Hepatitis and STI Programme); Dina Pfeifer (WHO Regional Office for Europe/Health

Emergencies Programme); Anayda Portela (Department of Maternal, Newborn, Child and Adolescent Health); Jacobus Preller (Clinical Team for COVID-19 Response); Andreas Reis (Global Health Ethics Team, Division of the Chief Scientist); Pryanka Relan (Integrated Health Services Department/Clinical Team for COVID-19 Response); Ludovic Reveiz (Evidence and Intelligence for Action in Health Department, Incident Management Systems for COVID-19, Pan American Health Organization); Lisa Rogers (Department of Nutrition for Health and Development); Nigel Rollins (Department of Maternal, Newborn, Child and Adolescent Health); Nicoline Schiess (Department of Mental Health and Substance Abuse); Katrin Seeher (Department of Mental Health and Substance Abuse); Ingrid Smith (WHO); Howard Sobel (WHO Regional Coordinator for Reproductive, Maternal, Newborn, Child and Adolescent Health); Maria Pura Solon (Methods and Standards, Quality Assurance of Norms and Standards Science Division); Yuka Sumi (Maternal, Newborn, Child and Adolescent Health and Ageing); Soumya Swaminathan (Office of Chief Scientist); Anna Thorson (Sexual and Reproductive Health and Research); Kavita Trivedi; Marco Vitoria (UHC, Communicable and NCDs); Prinzo Weise (Department of Healthier Population); Wilson Were (Maternal, Newborn, Child and Adolescent Health and Ageing); Pushpa Wijesinghe (Lead, case management, Regional Office for South-East Asia); Matteo Zignol (UHC, Communicable and NCD).

Supporting project officer: Jacqueline Lee Endt (Health Care Readiness Unit, Health Emergencies Department).

The WHO Steering Committee is fully responsible for decisions about guidance production and convening the GDG.

WHO convened GDG panel members: Wagdy Amin (Ministry of Health and Population, Egypt); Andre Ricardo Araujo da Silva (Federal Fluminense University, Brazil); Erlina Burhan (Infection Division Department of Pulmonology and Respiratory Medicine Faculty of Medicine Universitas Indonesia); Frederique Bausch (Geneva University Hospital, Switzerland); Darren Brown (Physiotherapy, Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom); Maurizio Cecconi (Humanitas Research Hospital Milan, Italy); Duncan Chanda (Adult Infectious Disease Centre, University Teaching Hospital, Lusaka, Zambia); Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Hanoi, Viet Nam); Bin Du (Peking Union Medical College Hospital, China); Heike Geduld (Emergency Medicine, Stellenbosch University, South Africa); Patrick Gee (patient panel member, United States); Madiha Hashmi (Ziauddin University, Karachi, Pakistan); Manai Hela (Emergency Medical Service Tunis, Tunisia); David Hui (Department of Medicine and Therapeutics, Stanley Ho Centre for Emerging Infectious Diseases, Chinese University of Hong Kong, Hong Kong SAR, China); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi India); Niranjan Kissoon (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Arthur Kwizera (Makerere College of Health Sciences, Kampala, Uganda); Yee-Sin Leo (National Centre for Infectious Diseases, Singapore); Thiago Lisboa (Coraçao Hospital, Sao Paulo, Brazil); Louise Thwaites (Oxford University Clinical Research Unit, Ho Chi Minh, Viet Nam); Swagata Tripathy (All India Institute of Medical Sciences, Bhubaneswar, India).

Methodologist: Gordon Guyatt (McMaster University, Canada).

Clinical Chairs: Neill Adhikari (Sunnybrook Health Sciences Centre and University of Toronto); Srinivas Murthy (Associate Professor, University of British Columbia, Vancouver, Canada).

We would like to acknowledge the **Guidance Support Collaboration Committee** which provided the coordination to allow the rapid development of the WHO guidance and its dissemination: Neill Adhikari (Sunnybrook Health Sciences Centre and University of Toronto); Lisa Askie (WHO); Janet V Diaz (WHO); Gordon Guyatt (McMaster University, Canada); Marta Lado (WHO); Srinivas Murthy (University of British Colombia, Canada); Jacobus Preller (WHO); Archana Seahwag (WHO); Joan B Soriano (WHO); and to the MAGIC Evidence Ecosystem Foundation for their support in the publication process through MAGICapp: Per Olav Vandvik, Arnav Agarwal, Lyubov Lytvyn, Stijn Rita Patrick van de Velde, Ying Wang, Linan Zeng, Dena Zeraatkar.

Special thanks to the following collaborators for providing systematic reviews:
National Institute for Health and Care Excellence (NICE), United Kingdom): COVID-19 rapid evidence review: management of the long-term effects of COVID-19, facilitated by Sara Buckner, Justine Karpusheff.

American Society of Hematology guideline/McMaster University GRADE Centre systematic review (www.hematology.org/COVIDguidelines) facilitated by Robby Nieuwlaat, Holger Schünemann (McMaster University, Canada).

Cochrane Library: Care bundles for improving outcomes in patients with COVID-19 in intensive care – a rapid scoping review, prepared by D Devane, A Nichol, D Roche, V Smith.

Karel GM Moons (University Medical Center Utrecht, www.covprecise.org); Maarten van Smeden (Utrecht); Laure Wynants (Leuven/Maastricht): COVID-19 related prediction models for prognosis: living systematic review.

Special thanks to experts who provided presentations to the GDG: Pasi Penttinen (European Centre for Disease Prevention and Control): Risk factors for severe outcomes following COVID-19 infection – results of a systematic literature review.

Special thanks to the WHO Rapid Review team and WHO Library: Thomas Allen (WHO Library); Haley Holmer (WHO Quality, Norms

and Standards); Ajay Rangaraj (WHO UHC, Communicable and NCDs); Vanessa Veronese (WHO Research and Training in Tropical Diseases) for conducting the evidence search.

Special thanks to the external reviewers for their insights on the new recommendations:
Richard Kojan (ALIMA and Teaching Hospital of Kinshasa, Democratic Republic of the Congo); Gabriel Alcoba, Francisco Bartolome, Marcio da Fonseca, Bhargavi Rao, Saschveen Singh, Armand Sprecher (Médecins Sans Frontières).

Special thanks to the following reviewers of the updates on Chapter 17 (neurological and mental manifestations): José Luis Ayuso-Mateos (Director, Department of Psychiatry, Universidad Autónoma de Madrid, CIBERSAM and WHO Collaborating Centre for Mental Health Services Research and Training, Spain); Corrado Barbui (WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Italy); Ettore Beghi (Professor of Neurology, Department of Neuroscience, Istituto di Ricerche Farmacologiche, Milano, Italy); Sherry H-Y Chou (Associate Professor of Critical Care Medicine, Neurology, and Neurosurgery, University of Pittsburgh School of Medicine, United States); Mario Maj (Director, Department of Psychiatry, University of Naples, Italy); Benedict Michael (Senior Clinician Scientist Fellow, Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom); Shubham Misra (Senior Research Fellow, Department of Neurology, All India Institute of Medical Sciences, New Delhi, India); Pratima Murthy (Professor and Head, Department of Psychiatry National Institute of Mental Health and Neuro-Sciences, Bangalore, India); Alessandro Padovani (Neurologist, Director, NeuroCOVID Unit, University of Brescia, Italy); Kameshwar Prasad (Professor of Neurology, All India Institute of Medical Sciences, New Delhi, India); Kiran Thakur (Neurologist, Winifred Mercer Pitkin Assistant Professor of Neurology, Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York City, United States).

Special thanks to the following reviewers of the updates on Chapter 19 (rehabilitation): Neelum Zehra Bukhari (Head, Department Occupational Therapy, Ziauddin College of Rehabilitation Sciences, Ziauddin University, Pakistan); Professor Trish Greenhalgh (Nuffield Department of Primary Care Health Sciences, University of Oxford, United Kingdom); Peter A Lim (Rehabilitation Medicine, Singapore General Hospital, Clinical Associate Professor, Duke-NUS Medical School, Singapore, and Clinical Professor, Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, United States); Professor Sally Singh (Head of Pulmonary and Cardiac Rehabilitation, University Hospitals Leicester, United Kingdom); Dr Abena Tannor (Rehabilitation Medicine, Komfo Anokye Teaching Hospital, Accra, Ghana).

Special thanks also go to the WHO COVID-19 IPC Global Expert Panel: April Baller (Infection Prevention and Control, WHE); Carole Fry (Infection Prevention and Control Hub and Task Force, Integrated Health Services, WHO).

Acknowledgements for *Clinical management of COVID-19: interim guidance* 27 May 2020

WHO Steering Committee: Janet V Diaz (Lead), Nazneen Anwar, Florence Baingana, April Baller, Anshu Banerjee, Silvia Bertagnolio, Mercedes Bonet, Andrea Bosman, Marie-Charlotte Bousseau, Andrea Bruni, Maurice Bucagu, Neerja Chowdhary, Jane Cunningham, Meg Doherty, Tarun Dua, Alexandra Fleichmann, Nathan Ford, Stéfanie Freel, Laurence Grummer-Strawn, Fahmy Hanna, Benedikt Huttner, Ernesto Jaramillo, Maria Van Kerkhove, Caron Kim, Kavitha Kolappa, Teresa Kortz, Ornella Lincetto, Aiysha Malik, Carmen Martinez, Alessandro Massazza, Jody-Ann Mills, Lorenzo Moja, Susan Norris, Olufemi Oladapo, Peter Olumese, Mark van Ommeren, Martina Penazzato, Anayda Portela, Andreas Reis, Pryanka Relan, Lisa Rogers, Nigel Rollins, Khalid Saeed, Katrin Seeher, Allison Schaefer, Nicoline Schiess, Ingrid Smith, Howard Sobel, Maria Pura Solon, Renato Souza, Yuka Sumi, Anna Thorson, Kavita Trivedi, Marco Vitoria, Prinzo Weise, Inka Weissbecker, Wilson Were, Matteo Zignol.

United Nations Children's Fund (UNICEF): Maya Arii.

Guideline Development Group members: Neill Adhikari (Sunnybrook Health Sciences Centre and University of Toronto); John Appiah (Senior Specialist, Paediatric Critical Care and Head of Paediatric Intensive Care Unit of the Komfo Anokye Teaching Hospital, Ghana); Florence Baingana (Research Fellow, Makerere University, Kampala, Uganda); Abdullah Balkhair (Head of Infectious Diseases Unit and Infection Control Department, Sultan Qaboos University, Oman); Lucille Blumberg (National Institute for Communicable Diseases, South Africa); Bin Cao (China-Japan Friendship Hospital, Capital Medical University, Beijing, China); Maurizio Cecconi (Head of Department Anesthesia and Intensive Care Units, Humanitas Research Hospital, Milan, Italy); Bronwen Connolly (Queen's University Belfast, United Kingdom); Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Viet Nam); Jake Dunning (Head of Emerging Infections and Zoonoses, Public Health England, United Kingdom); Rob Fowler (University of Toronto, Canada); Heike Geduld (African Federation for Emergency Medicine, Cape Town, South Africa); Charles Gomersall (Chinese University of Hong Kong, Hong Kong SAR, China); Rumina Hasan (Professor, Department of Pathology and Laboratory Medicine, Aga Kahn University, Pakistan, and Honorary Professor, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, United Kingdom); Manai Hela (Emergency Medical Service Tunis, Tunisia); David S Hui (Chairman of the Department of Medicine and Therapeutics, Chinese University of Hong Kong, Hong Kong SAR, China); Yae-Jean Kim (Sungkyunkwan University, Samsung Medical Center, Republic of Korea); Niranjan Kissoon (Professor in Critical Care, University of British Columbia and BC Children's Hospital, Vancouver, Canada);

Arthur Kwizera (Department of Anaesthesia and Critical Care, Makerere University, Kampala, Uganda); Pisake Lumbiganon (Director WHO Collaborating Centre for Research Synthesis in Reproductive Health, Faculty of Medicine, Khon Kaen University, Thailand); Flavia Machado (Anesthesiology, Pain and Intensive Care Department, Federal University of São Paulo, Brazil); Srinivas Murthy (Associate Professor, University of British Columbia, Vancouver, Canada); Saniya Sabzwari (Aga Khan University Hospital, Karachi, Pakistan); Rohit Sarin (Director, National Centre of Excellence Supranational TB Reference Laboratory, New Delhi, India); Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China); Maria Asuncion Silvestre (President, Kalusugan ng Mag-Ina [Health of Mother and Child], Quezon City, Philippines); João Paulo Souza (Professor of Public Health, Department of Social Medicine, Ribeirao Preto Medical School, University of São Paulo, Brazil).

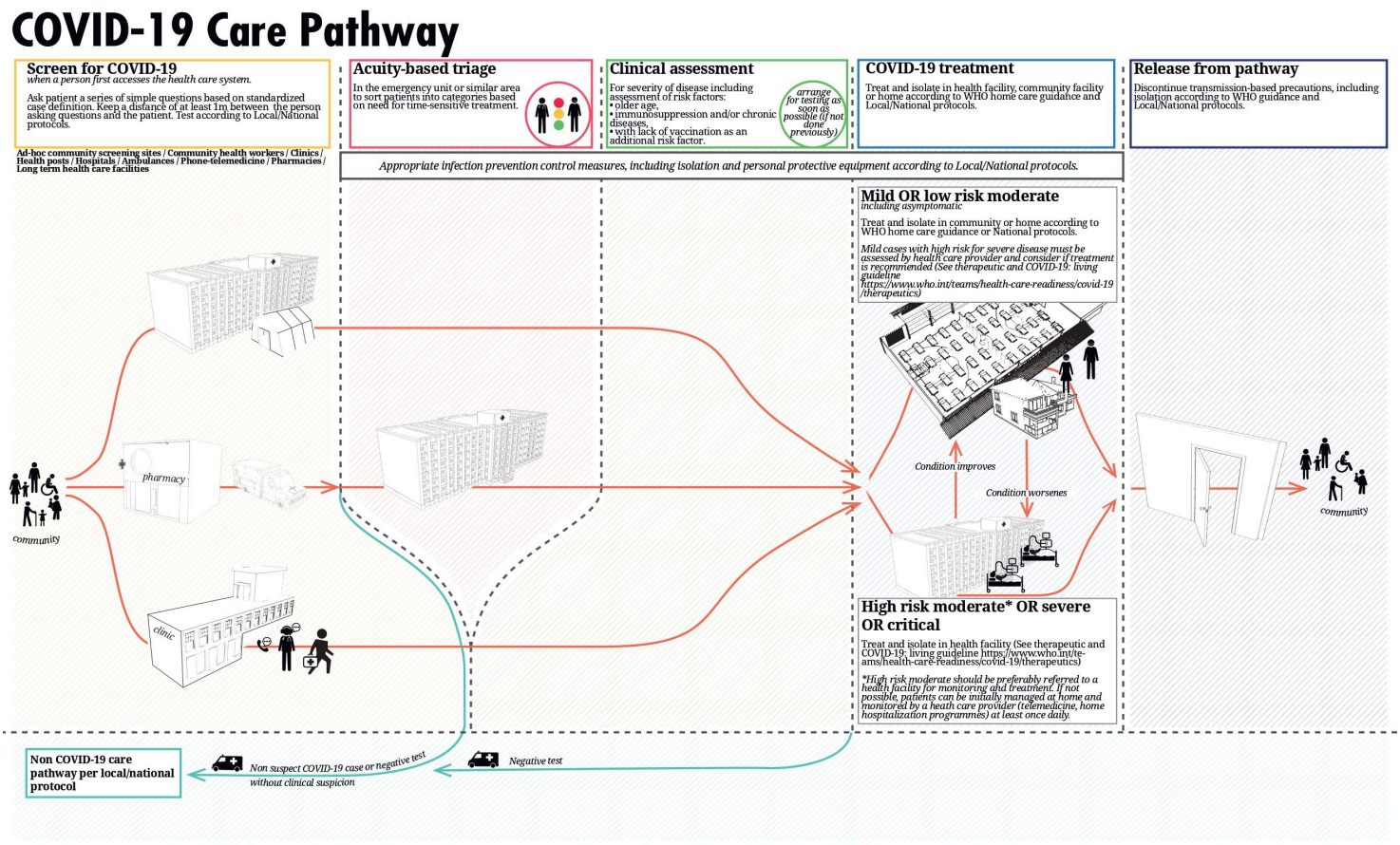
External reviewer panel: Francesco Castelli (Director, Department of Infectious and Tropical Diseases, University of Brescia and Brescia Civili General Hospital, Italy); Richard Kojan (ALIMA and Teaching Hospital of Kinshasa, Democratic Republic of the Congo); Benedict Michael (Senior Clinician Scientist Fellow, Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom); Shekhar Saxena (Professor, Department of Global Health and Population, Harvard TH Chan School of Public Health, Boston, United States).

External review of Chapter 17 (neurological and mental manifestations): José Luis Ayuso-Mateos (Director, Department of Psychiatry, Universidad Autónoma de Madrid, CIBERSAM and WHO Collaborating Centre for Mental Health Services Research and Training, Spain); Corrado Barbui (WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Italy); Rabih El Chammay (Director, National Mental Health Programme, Beirut, Lebanon); Oye Gureje (Director, Institute of Neurosciences, University College Hospital, Ibadan, Nigeria); Mario Maj (Director, Department of Psychiatry, University of Naples, Italy); Farrah Mateen (Associate Professor of Neurology, Harvard Medical School, Boston, United States); Pratima Murthy (Professor and Head, Department of Psychiatry National Institute of Mental Health and Neuro-Sciences, Bangalore, India); Giovanni Ostuzzi (Psychiatrist, University of Verona, Italy); Chuan Shi (Psychiatrist, University of Peking, Beijing, China); Felicia Smith (Psychiatrist, Massachusetts General Hospital, Harvard Medical School, Boston, United States); Graham Thornicroft (Professor of Community Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, and Health Service & Population Research Department, King's College London, United Kingdom); Peter Ventevogel (Senior Mental Health Advisor, United Nations High Commissioner for Refugees, Geneva, Switzerland).

Special thanks also go to the WHO COVID-19 IPC Global Expert Panel: Benedetta Allegranzi (Infection Prevention and Control Hub and Task Force, Integrated Health Services, WHO); April Baller (Infection Prevention and Control, WHE); Fernanda Lessa (US CDC (WHO secondment); Madison Moon (Infection Prevention and Control, WHE); Alice Simniceanu (Infection Prevention and Control, WHE).

Special thanks to the WHO Library: Thomas Allen (WHO Library) for conducting the evidence search.

ANNEX 1: COVID-19 care pathway



ANNEX 2: Resources for supporting clinical management of COVID-19

Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation (2020)
https://www.who.int/publications/i/item/clinical-care-of-severe-acute-respiratory-infections-tool-kit

IMAI District clinician manual: hospital care for adolescents and adults. Guidelines for the management of common illnesses with limited resources (2011)
The manual is written for clinicians working at the district hospital (first-level referral care) who diagnose and manage sick adolescents and adults in resource-constrained settings. It aims to support clinical reasoning, and to provide an effective clinical approach and protocols for the management of common and serious or potentially life-threatening conditions at district hospitals. The target audience includes doctors, clinical officers, health officers and senior nurse practitioners. It has been designed to be applicable in both high and low HIV prevalence settings.
https://www.who.int/hiv/pub/imai/imai2011/en/

WHO-ICRC Basic emergency care: approach to the acutely ill and injured (2018)
Developed by WHO and ICRC, in collaboration with the International Federation for Emergency Medicine, Basic emergency care (BEC): approach to the acutely ill and injured is an open-access training course for frontline health care providers who manage acute illness and injury with limited resources. The BEC package includes a Participant Workbook and electronic slide decks for each module. Integrating the guidance from WHO Emergency Triage, Assessment and Treatment (ETAT) for children and the Integrated Management of Adult/ Adolescent Illness (IMAI), BEC teaches a systematic approach to the initial assessment and management of time-sensitive conditions where early intervention saves lives.
https://www.who.int/publications/i/item/basic-emergency-care-approach-to-the-acutely-ill-and-injured

Pocket book of hospital care for children: guidelines for the management of common childhood illnesses (second edition) (2013)
For use by doctors, nurses, and other health workers caring for children at first-level referral hospitals with basic laboratory facilities and essential medicines. These guidelines focus on the management of the major causes of childhood mortality in most developing countries, including pneumonia, and also cover common procedures, patient monitoring, and supportive care on the wards. https://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/

Oxygen therapy for children (2016)
A bedside manual for health workers to guide the provision of oxygen therapy for children. The manual focuses on the availability and clinical use of oxygen therapy in children in health facilities to guide health workers, biomedical engineers and administrators. It addresses detection of hypoxaemia, use of pulse oximetry, clinical use of oxygen, delivery systems, and monitoring of patients on oxygen therapy. The manual also addresses the practical use of pulse oximetry, and oxygen concentrators and cylinders. http://www.who.int/maternal_child_adolescent/documents/child-oxygen-therapy/en/

Technical specifications for oxygen concentrators (2015)
Provides an overview of oxygen concentrators and technical specifications to aid in selection, procurement, and quality assurance. It highlights the minimum performance requirements and technical characteristics for oxygen concentrators and related equipment that are suitable for the use in health facilities. https://www.who.int/medical_devices/publications/tech_specs_oxygen-concentrators/en/

WHO-UNICEF technical specifications and guidance for oxygen therapy devices (2019)
The purpose of this document is to increase access to quality products to ensure the supply of oxygen, especially in low- and middle-income countries and low-resource settings within countries from all income groups. It aims to support ministries of health to ensure that oxygen supply is available, as well as to raise awareness of the importance of appropriate selection, procurement, maintenance, and use of medical devices, both capital equipment and single-use devices. https://www.who.int/medical_devices/publications/tech_specs_oxygen_therapy_devices/en/

WHO Priority medical devices list for the COVID-19 response and associated technical specifications (Nov 2020)
This document describes the medical devices required for the clinical management of COVID-19, selected and prioritized according to the latest available evidence and interim guidelines. This includes: oxygen therapy, pulse oximeters, patient monitors, thermometers, infusion and suction pumps, X-ray, ultrasound and CT scanners as well as personal protective equipment. In order to facilitate access to quality assured priority medical devices, the document also includes technical and performance characteristics, related standards, accessories and consumables. It is intended for policy-makers and planning officers in Ministries of Health, procurement and regulatory agencies, intergovernmental and international agencies as well as the medical device
industry.

https://www.who.int/publications/i/item/WHO-2019-nCoV-MedDev-TS-O2T.V2

Biomedical equipment for COVID-19 case management-inventory tool: Interim guidance (June 2020)
Countries can use this tool to collect in-depth facility inventories of biomedical equipment re-allocation, procurement and planning for COVID-19 case management. The survey assesses quantified availability and the causes for non-functioning of different sources of oxygen delivery and supply systems to the patient in order to determine priorities and re-allocation requirements in accordance with needs.

https://www.who.int/publications/i/item/WHO-2019-nCov-biomedical-equipment-inventory-2020.1

Implementation tools

Additional educational modules and implementation tools for health workers:

WHO COVID-19 essential supplies forecasting tool (COVID-ESFT) assists governments, partners, and other stakeholders to forecast the necessary volume of personal protective equipment, diagnostic test equipment, consumable medical supplies, biomedical equipment for case management, and essential drugs for supportive care and treatment of COVID-19.

WHO Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation provides algorithms and practical tools for clinicians working in acute care hospitals managing adult and paediatric patients with acute respiratory infection, including severe pneumonia, acute respiratory distress syndrome, sepsis and septic shock. This includes information on screening, testing, monitoring and treatments.

WHO Openwho.org clinical management course series hosts a full course series on COVID-19 which covers a holistic pathway of care for a patient, from screening and triage to rehabilitation, testing and treatments and palliative care.

WHO Priority medical device list for the COVID-19 response and associated technical specifications describes the technical and performance characteristics of medical devices used to manage patients with COVID-19, and also includes related standards for accessories and consumables. It is intended for policy-makers and planning officers in ministries of health, procurement and regulatory agencies, intergovernmental and international agencies as well as the medical device industry. For more information see WHO website on Health products and policy standards.

ANNEX 3: Search strategy (Section 11)

Search strategy exemplars – WHO NIV PICO 1

PICO 1 – DIRECT: Systematic and rapid reviews

Database	COVID-19 Global literature on coronavirus disease
URL	https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/
Search terms	"high flow oxygen" or "high-flow oxygen" or "highflow oxygen" or "high frequency oxygen" or "high-frequency oxygen" or "high flow cannula" or "high-flow cannula" or "highflow cannula" or "high frequency cannula" or "high-frequency cannula" or "high flow cannulae" or "high-flow cannulae" or "highflow cannulae" or "high frequency cannulae" or "high-frequency cannulae" or HFNC or HFOC or "HFN oxygen" or "HFN O2" or "nasal cannula" or "nasal cannulae" OR "high flow nasal" or "high-flow nasal" or "highflow nasal" or "high frequency nasal" or "high-frequency nasal" OR NIV or FNIV or "F-NIV" or HNIV or "H-NIV" OR "controlled ventilation" OR "continuous positive airway pressure" or "continuous positive air-way pressure" or "bilevel positive airway pressure" or "bilevel positive air-way pressure" or "bi-level positive airway pressure" or "bi-level positive air-way pressure" or "biphasic positive airway pressure" or "biphasic positive air-way pressure" or "bi-phasic positive airway pressure" or "bi-phasic positive air-way pressure" OR CPAP or nCPAP or BiPAP OR Vapotherm or Vapo-therm or Optiflow or Opti-flow or "transnasal insuDlation" or "trans-nasal insuDlation" or "Ambu Res-cue mask" or "Ambu Res-cue masks" or Easyfit or Performatrack or Performax or "transnasal mask" or "transnasal masks" or "trans-nasal mask" or "trans-nasal masks" OR "mechanical ventilation" or "mechanical respiration" or "artificial ventilation" or "artificial respiration" or "artificial airway" or "artificial air-way" or "artificial airways" or "artificial air-ways" OR "high frequency ventilation" or "high-frequency ventilation" OR "invasive ventilation" or IMV OR "airway pressure release" and ventilat* OR APRV OR

	"positive pressure breathing" AND inspiratory OR "positive pressure breathing" AND intermittent OR IPPB OR "fluoro-carbon" AND ventilat* OR fluorocarbon AND ventilat* OR "standard oxygen" or "standard O2" or "conventional oxygen" or "conventional O2" or "oxygen therapy" or "O2 therapy" or "oxygen inhalation therapy" or "O2 inhalation therapy" or "enriched air" OR "non-invasive" and oxygenat* OR noninvasive and oxygenat* OR "non-invasive" and ventilat* OR non-invasive and ventilat* OR Intubat* OR "endotracheal tube" or "endotracheal tubes" or "endotracheal tubation" or "endotracheal tubations" or "endotracheal ventilation" or "endo-tracheal tube" or "endo-tracheal tubes" or "endo-tracheal tubation" or "endo-tracheal tubations" or "endo-tracheal ventilation" OR tracheostom* OR tracheotom* (tw:("high flow oxygen" or "high-flow oxygen" or "highflow oxygen" or "high frequency oxygen" or "high-frequency oxygen" or "high flow cannula" or "high-flow cannula" or "highflow cannula" or "high frequency cannula" or "high-frequency cannula" or "high flow cannulae" or "high-flow cannulae" or "highflow cannulae" or "high frequency cannulae" or "high-frequency cannulae" or HFNC or HFOC or "HFN oxygen" or "HFN O2" or "nasal cannula" or "nasal cannulae")) OR (tw:("high flow nasal" or "high-flow nasal" or "highflow nasal" or "high frequency nasal" or "high-frequency nasal")) OR (tw:(NIV or FNIV or "F-NIV" or HNIV or "H-NIV")) OR (tw:("non-invasive" and oxygenat*)) OR (tw:(noninvasive and oxygenat*)) OR (tw:("non-invasive" and ventilat*)) OR (tw:(non-invasive and ventilat*)) OR (tw:("controlled ventilation")) OR (tw:("continuous positive airway pressure" or "continuous positive air-way pressure" or "bilevel positive airway pressure" or "bilevel positive air-way pressure" or "bi-level positive airway pressure" or "bi-level positive air-way pressure" or "biphasic positive airway pressure" or "biphasic positive air-way pressure" or "bi-phasic positive airway pressure" or "bi-phasic positive air-way pressure")) OR (tw:(CPAP or nCPAP or BiPAP)) OR (tw:(Vapotherm or Vapo-therm or Optiflow or Opti-flow or "transnasal insuDlation" or "trans-nasal insuDlation" or "Ambu Res-

	cue mask" or "Ambu Res-cue masks" or Easyfit or Performatrack or Performax or "transnasal mask" or "transnasal masks" or "trans-nasal mask" or "trans-nasal masks")) OR (tw:("mechanical ventilation" or "mechanical respiration" or "artificial ventilation" or "artificial respiration" or "artificial airway" or "artificial air-way" or "artificial airways" or "artificial air-ways")) OR (tw:("high frequency ventilation" or "high-frequency ventilation")) OR (tw:("invasive ventilation" or IMV)) OR (tw:("airway pressure release" and ventilat*)) OR (tw:(APRV)) OR (tw:("positive pressure breathing" AND inspiratory)) OR (tw:("positive pressure breathing" AND intermittent)) OR (tw:(IPPB)) OR (tw:("fluoro-carbon" AND ventilat*)) OR (tw:(fluorocarbon AND ventilat*)) OR (tw:("standard oxygen" or "standard O2" or "conventional oxygen" or "conventional O2" or "oxygen therapy" or "O2 therapy" or "oxygen inhalation therapy" or "O2 inhalation therapy" or "enriched air")) OR (tw:(intubat*)) OR (tw:("endotracheal tube" or "endotracheal tubes" or "endotracheal tubation" or "endotracheal tubations" or "endotracheal ventilation" or "endo-tracheal tube" or "endo-tracheal tubes" or "endo-tracheal tubation" or "endo-tracheal tubations" or "endo-tracheal ventilation")) OR (tw:(tracheostom* OR tracheotom*)) Refined by: Systematic Review, Evidence Synthesis, Broad Synthesis TOTAL: 287 records
Study types	Systematic or rapid reviews
Search date	3 May 2021

PICO 1 – DIRECT: Top-up of RCTs since last SR search date

Database	COVID-19 Global literature on coronavirus disease
URL	https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/
Search terms	"high flow oxygen" or "high-flow oxygen" or "highflow oxygen" or "high frequency oxygen" or "high-frequency oxygen" or "high flow cannula" or "high-flow cannula" or "highflow cannula" or "high frequency cannula" or "high-frequency cannula" or "high flow cannulae" or "high-flow cannulae" or "highflow cannulae" or "high frequency cannulae" or "high-frequency cannulae" or HFNC or HFOC or "HFN oxygen" or "HFN O2" or "nasal cannula" or "nasal cannulae" OR "high flow nasal" or "high-flow nasal" or "highflow nasal" or "high frequency nasal" or "high-frequency nasal" OR NIV or FNIV or "F-NIV" or HNIV or "H-NIV" OR "controlled ventilation" OR "continuous positive airway pressure" or "continuous positive air-way pressure" or "bilevel positive airway pressure" or "bilevel positive air-way pressure" or "bi-level positive airway pressure" or "bi-level positive air-way pressure" or "biphasic positive airway pressure" or "biphasic positive air-way pressure" or "bi-phasic positive airway pressure" or "bi-phasic positive air-way pressure" OR CPAP or nCPAP or BiPAP OR

	Vapotherm or Vapo-therm or Optiflow or Opti-flow or "transnasal insuDlation" or "trans-nasal insuDlation" or "Ambu Res-cue mask" or "Ambu Res-cue masks" or Easyfit or Performatrack or Performax or "transnasal mask" or "transnasal masks" or "trans-nasal mask" or "trans-nasal masks" OR "mechanical ventilation" or "mechanical respiration" or "artificial ventilation" or "artificial respiration" or "artificial airway" or "artificial air-way" or "artificial airways" or "artificial air-ways" OR "high frequency ventilation" or "high-frequency ventilation" OR "invasive ventilation" or IMV OR "airway pressure release" and ventilat* OR APRV OR "positive pressure breathing" AND inspiratory OR "positive pressure breathing" AND intermittent OR IPPB OR "fluoro-carbon" AND ventilat* OR fluorocarbon AND ventilat* OR "standard oxygen" or "standard O2" or "conventional oxygen" or "conventional O2" or "oxygen therapy" or "O2 therapy" or "oxygen inhalation therapy" or "O2 inhalation therapy" or "enriched air" OR "non-invasive" and oxygenat* OR noninvasive and oxygenat* OR "non-invasive" and ventilat* OR non-invasive and ventilat* OR

	Intubat* OR "endotracheal tube" or "endotracheal tubes" or "endotracheal tubation" or "endotracheal tubations" or "endotracheal ventilation" or "endo-tracheal tube" or "endo-tracheal tubes" or "endo-tracheal tubation" or "endo-tracheal tubations" or "endo-tracheal ventilation" OR tracheostom* OR tracheotom* (tw:("high flow oxygen" or "high-flow oxygen" or "highflow oxygen" or "high frequency oxygen" or "high-frequency oxygen" or "high flow cannula" or "high-flow cannula" or "highflow cannula" or "high frequency cannula" or "high-frequency cannula" or "high flow cannulae" or "high-flow cannulae" or "highflow cannulae" or "high frequency cannulae" or "high-frequency cannulae" or HFNC or HFOC or "HFN oxygen" or "HFN O2" or "nasal cannula" or "nasal cannulae")) OR (tw:("high flow nasal" or "high-flow nasal" or "highflow nasal" or "high frequency nasal" or "high-frequency nasal")) OR (tw:(NIV or FNIV or "F-NIV" or HNIV or "H-NIV")) OR (tw:("non-invasive" and oxygenat*)) OR (tw:(noninvasive and oxygenat*)) OR (tw:("non-invasive" and ventilat*)) OR (tw:(non-invasive and ventilat*)) OR (tw:("controlled ventilation")) OR (tw:("continuous positive airway pressure" or "continuous positive air-way pressure" or "bilevel positive airway pressure" or "bilevel positive air-way pressure" or "bi-level positive airway pressure" or "bi-level positive air-way pressure" or "biphasic positive airway pressure" or "biphasic positive air-way pressure" or "bi-phasic positive airway pressure" or "bi-phasic positive air-way pressure")) OR (tw:(CPAP or nCPAP or BiPAP)) OR (tw:(Vapotherm or Vapo-therm or Optiflow or Opti-flow or "transnasal insuDlation" or "trans-nasal insuDlation" or "Ambu Res-cue mask" or "Ambu Res-cue masks" or Easyfit or Performatrack or Performax or "transnasal mask" or "transnasal masks" or "trans-nasal mask" or "trans-nasal masks")) OR (tw:("mechanical ventilation" or "mechanical respiration" or "artificial ventilation" or "artificial respiration" or "artificial airway" or "artificial air-way" or "artificial airways" or "artificial air-ways")) OR (tw:("high frequency ventilation" or "high-frequency ventilation")) OR (tw:("invasive ventilation" or IMV)) OR (tw:("airway pressure release" and ventilat*)) OR (tw:(APRV)) OR (tw:("positive pressure breathing" AND inspiratory)) OR (tw:("positive pressure breathing" AND intermittent)) OR (tw:(IPPB)) OR (tw:("fluoro-carbon" AND ventilat*)) OR (tw:(fluorocarbon AND ventilat*)) OR (tw:("standard oxygen" or "standard O2" or "conventional oxygen" or "conventional O2" or "oxygen therapy" or "O2 therapy" or "oxygen inhalation therapy" or "O2 inhalation therapy" or "enriched air")) OR (tw:(intubat*)) OR (tw:("endotracheal tube" or "endotracheal tubes" or "endotracheal tubation" or "endotracheal tubations" or "endotracheal ventilation" or "endo-tracheal tube" or "endo-tracheal tubes" or "endo-tracheal tubation" or "endo-tracheal tubations" or "endo-tracheal ventilation")) OR (tw:(tracheostom* OR tracheotom*)) Refined by: Controlled Clinical Trial, Year 2020-2021 504 results
Study types	Randomized and non-randomized studies of interventions
Search date	17 June 2021 (alerts continued to Dec 2021, ongoing studies were all checked for results or status changes to same date)

PICO 1 – INDIRECT: Systematic and rapid reviews

Database	Epistemonikos
URL	https://www.epistemonikos.org/
Search terms	(advanced_title_en:(ventilat* OR cannula* OR HFNC OR HFOC OR "HFN oxygen" OR "HFN O2" OR NIV OR FNIV OR "F-NIV" OR HNIV OR "H-NIV" OR "positive airway pressure" OR ""positive air-way pressure" OR CPAP OR nCPAP OR BiPAP OR "high flow oxygen" OR "highflow oxygen" OR "high frequency oxygen" OR oxygenat* OR "high flow nasal" OR "high-flow nasal" OR "highflow nasal" OR "high frequency nasal" OR "transnasal mask" OR "transnasal masks" OR "trans-nasal mask" OR "trans-nasal masks" OR IMV OR "mechanical respiration" OR "artificial respiration" OR "artificial airway" OR "artificial air-way" OR "artificial airways" OR "artificial air-ways" OR "airway pressure release" OR APRV OR "positive pressure breathing" OR "standard oxygen" OR "standard O2" OR "conventional oxygen" OR "conventional O2" OR "oxygen therapy" OR "O2 therapy" OR "oxygen inhalation therapy" OR "O2 inhalation therapy" OR "enriched air" OR

	intubat* OR tubation* OR tube OR tubes OR tracheostom* OR tracheotom*) OR advanced_abstract_en:(ventilat* OR cannula* OR HFNC OR HFOC OR "HFN oxygen" OR "HFN O2" OR NIV OR FNIV OR "F-NIV" OR HNIV OR "H-NIV" OR "positive airway pressure" OR ""positive air-way pressure" OR CPAP OR nCPAP OR BiPAP OR "high flow oxygen" OR "highflow oxygen" OR "high frequency oxygen" OR oxygenat* OR "high flow nasal" OR "high-flow nasal" OR "highflow nasal" OR "high frequency nasal" OR "transnasal mask" OR "transnasal masks" OR "trans-nasal mask" OR "trans-nasal masks" OR IMV OR "mechanical respiration" OR "artificial respiration" OR "artificial airway" OR "artificial air-way" OR "artificial airways" OR "artificial air-ways" OR "airway pressure release" OR APRV OR "positive pressure breathing" OR "standard oxygen" OR "standard O2" OR "conventional oxygen" OR "conventional O2" OR "oxygen therapy" OR "O2 therapy" OR "oxygen inhalation therapy" OR "O2 inhalation therapy" OR "enriched air" OR intubat* OR tubation* OR tube OR tubes OR tracheostom* OR tracheotom*)) AND (advanced_title_en:((advanced_title_en:(acute respiratory distress) OR advanced_abstract_en:(acute respiratory distress)) OR (advanced_title_en:(ards) OR advanced_abstract_en:(ards)) OR (advanced_title_en:(acute hypoxemic respiratory failure) OR advanced_abstract_en:(acute hypoxemic respiratory failure)) OR (advanced_title_en:(acute hypoxaemic respiratory failure) OR advanced_abstract_en:(acute hypoxaemic respiratory failure)) OR (advanced_title_en:(AHRF) OR advanced_abstract_en:(AHRF)) OR (advanced_title_en:(shock lung) OR advanced_abstract_en:(shock lung))) OR advanced_abstract_en:((advanced_title_en:(acute respiratory distress) OR advanced_abstract_en:(acute respiratory distress)) OR (advanced_title_en:(ards) OR advanced_abstract_en:(ards)) OR (advanced_title_en:(acute hypoxemic respiratory failure) OR advanced_abstract_en:(acute hypoxemic respiratory failure)) OR (advanced_title_en:(acute hypoxaemic respiratory failure) OR advanced_abstract_en:(acute hypoxaemic respiratory failure)) OR (advanced_title_en:(AHRF) OR advanced_abstract_en:(AHRF)) OR (advanced_title_en:(shock lung) OR advanced_abstract_en:(shock lung)))) [Filters: protocol=no, classification=systematic-review]
Study types	Systematic or rapid reviews
Search date	18 May 2021

PICO 1 – INDIRECT: Top-up of RCTs since last SR search date

Database	EBM Reviews - Cochrane Central Register of Controlled Trials
URL	https://www.wolterskluwer.com/en/solutions/ovid/evidencebased-medicine-reviews-ebmr-904
Search terms	1 respiratory distress syndrome, adult/ (37) 2 ((respiratory or respiration or lung or ventilatory) adj2 (depress* or insufficien* or fail* or deficien* or disturb* or dysfunction* or compromis*) adj3 (acute or adult)).ti,ab,kw. (1910) 3 (lung adj1 shock).ti,ab,kw. (10) 4 ARDS.ti,ab,kw. (2155) 5 ARDSS.ti,ab,kw. (0) 6 exp Respiratory Insufficiency/ (2829) 7 (respiratory failure adj3 hypox?emi*).ti,ab,kw. (404) 8 (respiratory failure adj3 hypercapni*).ti,ab,kw. (327) 9 AHRF.ti,ab,kw. (90) 10 (acute adj2 (hypoxia or hypox?emi*)).ti,ab,kw. (670) 11 or/1-10 [ARDS/AHRF] (6797) 12 Cannula/ (113) 13 Oxygen/ (5200) 14 Oxygen Inhalation Therapy/ (1164) 15 11 and (13 or 14) (456)

	16 ((high-flow or highflow or high-frequency or prolong*) adj3 cannula*).ti,ab,kw. (908) 17 ((high-flow or highflow or high-frequency or prolong*) adj3 nasal*).ti,ab,kw. (1332) 18 ((high-flow or highflow or high-frequency or prolong*) adj3 (oxygen* or O2)).ti,ab,kw. (1097) 19 (HFNC or HFNO or HFNP or HFOC).ti,ab,kw. (561) 20 (("positive pressure" or "positive end-expiratory pressure") adj3 (respirat* or ventilat*)).ti,ab,kw. (2211) 21 continuous positive airway pressure.ti,ab,kw. (3829) 22 (CPAP or nCPAP).ti,ab,kw. (5110) 23 (airway pressure release adj3 ventilat*).ti,ab,kw. (80) 24 APRV.ti,ab,kw. (69) 25 ((inspiratory or intermittent) adj3 positive pressure breathing).ti,ab,kw. (75) 26 IPPB.ti,ab,kw. (69) 27 ((non-invasive or noninvasive) adj3 (oxygen* or ventilat*)).ti,ab,kw. (3456) 28 controlled ventilation.ti,ab,kw. (849) 29 (bi level positive airway pressure or bilevel positive airway pressure or bi-level positive airway pressure or BiPaP or NIV).ti,ab,kw. (1635) 30 (FNIV or F-NIV or H-NIV or HNIV).ti,ab,kw. (20) 31 standard oxygen.ti,ab,kw. (206) 32 ((low flow or low-flow or lowflow) adj2 oxygen*).ti,ab,kw. (206) 33 ((mask* or helmet*) adj1 (face or oxygen)).ti,ab,kw. (1826) 34 (Ambu Res-cue mask* or Easyfit or Performatrack or Performax or transnasal mask* or facemask* or face-mask*).ti,ab,kw. (2042) 35 controlled ventilation.ti,ab,kw. (849) 36 exp Respiration, Artificial/ (6241) 37 exp Ventilators, Mechanical/ (268) 38 ((artificial* or mechanical*) adj3 (respirat* or ventilat*)).ti,ab,kw. (15417) 39 artificial airway?.ti,ab,kw. (98) 40 ((assist* or depend* or support*) adj3 (respirat* or ventilat*)).ti,ab,kw. (5925) 41 ((liquid or fluorocarbon or fluoro-carbon) adj3 ventilat*).ti,ab,kw. (42) 42 (high-frequency adj3 ventilat*).ti,ab,kw. (569) 43 (invasive* adj3 (oxygen* or ventilat*)).ti,ab,kw. (3149) 44 [IMV.tw,kf.] (0) 45 or/15-44 [VENTILATION OPTIONS] (30378) 46 11 and 45 [ARDS/AHRF - VENTILATION OPTIONS] (3698) 47 (202012* or 2021*).up. (642312) 48 46 and 47 [UPDATE PERIOD] (1817)
Study types	Randomized studies published after the date of the last indirect PICO SR or RR search (December 1, 2020

	based on included SR)
Search date	Dec 1 2020 to 1 Jun 2021 (alerts continued to Dec 2021)

ANNEX 4: Description of included studies (Section 11)

Direct PICO: Severe or critical COVID-19 patients with acute hypoxaemic respiratory failure and not requiring emergent intubation:

Five randomized controlled trials (RCTs) of non-invasive ventilation strategies in hospitalized patients with severe or critical COVID-19 and acute hypoxaemic respiratory failure not requiring emergent intubation were identified *(74)(235)(230)(75)(233)*. This evidence was collected using the included study lists of **three relevant systematic reviews, four rapid reviews, and a top-up search** of bibliographic databases for more recent RCTs (with alerts until December 2021) *(237)*.

Summary of included RCTs:

Study/ Design	Population	Country/ Setting	Interventions	Outcomes reported
Li et al. 2020 *(75)* two-arm, parallel RCT N=72	Patients with severe coronavirus pneumonia complicated with acute respiratory failure	China, isolation ward of a single centre	HFNO [n=37] Standard oxygen therapy [n=35]	Mechanical ventilation at 12 h No patient-reported outcomes
Grieco et al. 2021 *(235)* HENIVOT two-arm, parallel RCT N=109	Patients admitted to the intensive care unit with COVID-19–induced moderate to severe hypoxaemic respiratory failure	Italy, ICUs in four centres	Helmet NIV [n=55] HFNO [n=54]	Intubation, 28 d Hospital LOS ICU LOS Patient-reported: Device-related discomfort
Perkins et al. 2021 *(233)* RECOVERY-RS three-arm, adaptive RCT N=1272	Hospitalized adults with acute respiratory failure due to COVID-19 were deemed suitable for tracheal intubation if treatment escalation was required	United Kingdom, 75 hospitals	CPAP [n=380] HFNO [n=417] Standard oxygen therapy [n=475] (primary comparisons were CPAP to standard oxygen and HFNO to standard oxygen)	Mortality, 30 d Intubation, 30 d Tracheal intubation during the study period

Study/ Design	Population	Country/ Setting	Interventions	Outcomes reported
				Critical care (ICU) LOS Hospital LOS No patient-reported outcomes
Teng et al. 2021 *(74)* two-arm, parallel RCT N= 22	Patients diagnosed with severe COVID-19.	China, single centre	HFNO [n=12] Standard oxygen therapy [n=10]	Mortality (indirect) Hospital LOS ICU LOS No patient-reported outcomes
Ospina-Tascón et al. 2021 *(230)* Two-arm, open-label parallel RCT N=199	Adult patients admitted to the emergency department, general ward, or intensive care unit with acute respiratory failure and COVID-19	Colombia, three centres	HFNO [n=99] Standard oxygen therapy [n=100]	Mortality, 28 d Intubation, 28 d Hospital LOS ICU LOS No patient-reported outcomes

d=days; h=hours; HFNO=high flow nasal oxygen; ICU=intensive care unit; LOS=length of stay; RCT=randomized controlled trial; QoL=quality of life.

Indirect PICO: Non-COVID-19 ARDS patients with acute hypoxaemic respiratory failure not requiring emergent intubation

22 completed randomized controlled trials (RCTs) from 24 reports of non-invasive ventilation support in hospitalized patients with acute respiratory distress syndrome (ARDS) and acute hypoxaemic respiratory failure (AHRF) not requiring emergent intubation were identified *(237)*.

This evidence was collected using the included study lists of **four systematic reviews (SRs)** *(237)***. A top-up search** of study registry databases found no additional eligible RCTs. None of the included SRs included RCTs relevant to the indirect PICO with patient-reported outcomes such as comfort or satisfaction with care.

ANNEX 5: Case definitions of MIS-C (Section 14)

Organization	Case definition
World Health Organization	1. Age 0 to 19 years; AND 2. Fever for ≥ 3 days; AND 3. Clinical signs of multisystem involvement (at least two of the following): • rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet); • hypotension or shock; • cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP); • evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer); • acute gastrointestinal symptoms (diarrhoea, vomiting, or abdominal pain); AND 4. Elevated markers of inflammation (e.g. ESR, CRP, or procalcitonin); AND 5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/ streptococcal toxic shock syndromes; AND 6. Evidence of SARS-CoV-2 infection with ANY of the following: positive SARS-CoV-2 RT-PCR; positive serology; positive antigen test; contact with an individual with COVID-19.
US CDC	1. Individual < 21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥ 2) organ involvement (cardiac, renal, respiratory, haematologic, gastrointestinal, dermatologic or neurological); AND 2. No alternative plausible diagnoses; AND 3. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.
Royal College of Paediatrics and Child Health (RCPCR)	1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single- or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features. This may include children fulfilling full or partial criteria for Kawasaki disease. 2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus. 3. SARS-CoV-2 PCR testing may be positive or negative.

ANNEX 6: Guideline pruning (restructuring)

The summary table is available here *(581)*.

References

1. Operational considerations for case management of COVID-19 in health facility and community: interim guidance, 19 March 2020. Geneva: World Health Organization; 2020 (https://iris.who.int/handle/10665/331492, accessed 15 August 2024) Website

2. World Health Organization. Country & technical guidance – coronavirus disease (COVID-19). 2020. Website

3. Gao YA, Zhao Y, Zhang XI, Tian J, Guyatt G, Hao Q. Comparison of different isolation periods for preventing the spread of COVID-19: a rapid systematic review and a modelling study. 2023. Journal Website

4. Weekly epidemiological update on COVID-19 - 27 April 2023. Geneva: World Health Organization; 2023 (https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---27-april-2023, accessed 5/6/2023). Website

5. Coronavirus (COVID-19) Vaccinations [online resource]. Our World in Data; 2021 (https://ourworldindata.org/covid-vaccinations, accessed 20 March 2021). Website

6. Naci H, Kesselheim AS, Røttingen J-A, Salanti G, Vandvik PO, Cipriani A. Producing and using timely comparative evidence on drugs: lessons from clinical trials for covid-19. bmj 2020;371

7. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci AM, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis. PLoS medicine 17(9):e1003346 Pubmed Journal

8. Byambasuren O, Cardona M, Bell K. Estimating the extent of true asymptomatic COVID-19 and its potential for community transmission: systematic review and meta-analysis. Available at SSRN 3586675. 2020 Apr 23.

9. Yanes-Lane M, Winters N, Fregonese F, Bastos M, Perlman-Arrow S, Campbell JR, et al. Proportion of asymptomatic infection among COVID-19 positive persons and their transmission potential: A systematic review and meta-analysis. PloS one 15(11):e0241536 Pubmed Journal

10. Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin 2020;25(10) Pubmed Journal

11. Alene M, Yismaw L, Assemie MA, Ketema DB, Mengist B, Kassie B, et al. Magnitude of asymptomatic COVID-19 cases throughout the course of infection: A systematic review and meta-analysis. PloS one 16(3):e0249090 Pubmed Journal

12. Clarke C, Prendecki M, Dhutia A, Ali MA, Sajjad H, Shivakumar O, et al. High Prevalence of Asymptomatic COVID-19 Infection in Hemodialysis Patients Detected Using Serologic Screening. Journal of the American Society of Nephrology : JASN 2020;31(9):1969-1975 Pubmed Journal

13. The novel coronavirus pneumonia emergency response epidemiology team. Vital Surveillances: the epidemiological characteristics of an outbreak of 2019 Novel Coronavirus diseases (COVID-19)-China 2020. China CDC weekly 2020;2(8):113-22

14. Spinato G., Fabbris C., Polesel J., Cazzador D., Borsetto D., Hopkins C., et al. Alterations in Smell or Taste in Mildly Symptomatic Outpatients With SARS-CoV-2 Infection. JAMA 2020. Pubmed Journal Website

15. Favas TT, Dev P, RN C. Neurological manifestations of COVID-19: a systematic review and meta-analysis of proportions. Neurological Sciences 2020. Journal

16. Abdullahi A, Candan SA, Abba MA. Neurological and musculoskeletal features of COVID-19: a systematic review and meta-analysis. Frontiers in Neurology 2020;11:687

17. Kantonen J, Mahzabin S, Mäyränpää MI. Neuropathologic features of four autopsies COVID-19 patients. Letter to the editor. Brain Pathology 2020. Journal

18. Koutroumanidis M, Gratwicke J, Sharma S. Alpha coma EEG pattern in patients with severe COVID-19 related encephalopathy. Clinical Neurophysiology 2020;S1388-2457(0):30480-6 Journal

19. Neurology and COVID-19: Scientific brief. 2021. Website

20. Liu N., Sun J., Wang X., Zhao M., Huang Q., Li H.. The Impact of Dementia on the Clinical Outcome of COVID-19: A Systematic Review and Meta-Analysis. J Alzheimers Dis 78(4):1775-1782 Pubmed Journal

21. COVID-19 and Mental Health: Early evidence of. Website

22. A clinical case definition of post COVID-19 condition by a Delphi consensus. 2021. Website

23. Crivelli L., Palmer K., Calandri I., Guekht A., Beghi E., Carroll W., et al. Changes in cognitive functioning after COVID-19: A systematic review and meta-analysis. Alzheimers Dement 18(5):1047-1066 Pubmed Journal

24. Mao L., Jin H., Wang M., Hu Y., Chen S., He Q., et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020. Pubmed Journal Website

25. Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62354 COVID-19 cases in the USA. Lancet Psychiatry 2020;S2215-0366(20):30462-4 Journal

26. Liotta EM, Batra A, Clark JR, Shlobin NA, Hoffman SC, Orban ZS, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Annals of Clinical and Translational Neurology 2020;7(11):2221-2230 Journal

27. Helms J., Kremer S., Merdji H., Clere-Jehl R., Schenck M., Kummerlen C., et al. Neurologic Features in Severe SARS-CoV-2 Infection. N Engl J Med 2020. Pubmed Journal Website

28. Chen T., Wu D., Chen H., Yan W., Yang D., Chen G., et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1091 Pubmed Journal Website

29. Oxley TJ, Mocco J., Majidi S., Kellner CP, Shoirah H., Singh IP, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. N Engl J Med 2020. Pubmed Journal Website

30. Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020. Pubmed Journal Website

31. Varatharaj A, Thomas N, Ellul MA. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry 2020;7(10):875-882 Journal

32. Zhao H., Shen D., Zhou H., Liu J., Chen S.. Guillain-Barre syndrome associated with SARS-CoV-2 infection: causality or coincidence?. Lancet Neurol 2020;19(5):383-384 Pubmed Journal Website

33. Poyiadji N., Shahin G., Noujaim D., Stone M., Patel S., Griffith B.. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. Radiology 2020;201187 Pubmed Journal Website

34. Nanda S, Handa R, Prasad A, Anand R, Zutshi D, Dass SK, et al. COVID-19 associated Guillain-Barre Syndrome: Contrasting tale of four patients from a tertiary care centre in India. Am J Emerg Med 2020;39:125-8 Journal

35. Viner RM, Ward JL, Hudson LD, Ashe M., Patel SV, Hargreaves D., et al. Systematic review of reviews of symptoms and signs of

COVID-19 in children and adolescents. Arch Dis Child Pubmed Journal

36. Liguoro I., Pilotto C., Bonanni M., Ferrari ME, Pusiol A., Nocerino A., et al. SARS-COV-2 infection in children and newborns: a systematic review. Eur J Pediatr 2020;179(7):1029-1046 Pubmed Journal

37. Forrest CB, Burrows EK, Mejias A, Razzaghi H, Christakis D, Jhaveri R, et al. Severity of Acute COVID-19 in Children <18 Years Old March 2020 to December 2021. Pediatrics 2022;149(4):e2021055765 Journal Website

38. Buitrago-Garcia D., Egli-Gany D., Counotte MJ, Hossmann S., Imeri H., Ipekci AM, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis. PLoS Med 17(9):e1003346 Pubmed Journal

39. Irfan O., Muttalib F., Tang K., Jiang L., Lassi ZS, Bhutta Z.. Clinical characteristics, treatment and outcomes of paediatric COVID-19: a systematic review and meta-analysis. Arch Dis Child 106(5):440-8 Pubmed Journal

40. Ma X., Liu S., Chen L., Zhuang L., Zhang J., Xin Y.. The clinical characteristics of pediatric inpatients with SARS-CoV-2 infection: A meta-analysis and systematic review. J Med Virol 2021;93(1):234-240 Pubmed Journal

41. Ng KF, Bandi S., Bird PW, Wei-Tze Tang J.. COVID-19 in Neonates and Infants: Progression and Recovery. Pediatr Infect Dis J 2020;39(7):e140-e142 Pubmed Journal

42. Bhopal SS, Bagaria J., Olabi B., Bhopal R.. Children and young people remain at low risk of COVID-19 mortality. Lancet Child Adolesc Health 2021;5(5):e12-e13 Pubmed Journal

43. Whittaker E., Bamford A., Kenny J., Kaforou M., Jones CE, Shah P., et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. Jama 2020;324(3):259-269 Pubmed Journal

44. Abrams JY, Oster ME, Godfred-Cato SE, Bryant B., Datta SD, Campbell AP, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. Lancet Child Adolesc Health 2021;5(5):323-331 Pubmed Journal

45. Riphagen S., Gomez X., Gonzalez-Martinez C., Wilkinson N., Theocharis P.. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020. Pubmed Journal Website

46. Kaushik A, Gupta S, Sood M, Sharma S, Verma S. A Systematic Review of Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 Infection. The Pediatric infectious disease journal 2020;39(11):e340-e346 Pubmed Journal

47. Swann OV, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. BMJ 2020;370:m3249 Journal Website

48. Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, et al. Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19. JAMA 2021;325(11):1074-1087 Journal Website

49. Godfred-Cato S., Bryant B., Leung J., Oster ME, Conklin L., Abrams J., et al. COVID-19-Associated Multisystem Inflammatory Syndrome in Children - United States, March-July 2020. MMWR Morb Mortal Wkly Rep 2020;69(32):1074-1080 Pubmed Journal

50. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ 370:m3320 Journal Website

51. EDIT. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. Website

52. Emergency use ICD codes for COVID-19 disease outbreak. (https://www.who.int/standards/classifications/classification-of-diseases/emergency-use-icd-codes-for-covid-19-disease-outbreak, accessed 12 January 2020)

53. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of

COVID-19: a retrospective cohort study using electronic health records. The Lancet Psychiatry 2021;8(5):416-427

54. Domingo FR, Waddell LA, Cheung AM, Cooper CL, Belcourt VJ, Zuckermann AM, et al. Prevalence of long-term effects in individuals diagnosed with COVID-19: a living systematic review. medRxiv 2021.

55. Tracking of Variants. Website

56. Vandvik PO, Brandt L, Alonso-Coello P, Treweek S, Akl EA, Kristiansen A, et al. Creating clinical practice guidelines we can trust, use, and share: a new era is imminent. Chest 2013;144(2):381-389 Pubmed Journal

57. World Health Organization. WHO Handbook for guideline development. 2nd Edition. Website

58. Rochwerg B, Siemieniuk RA, Agoritsas T, Lamontagne F, Askie L, Lytvyn L, et al. A living WHO guideline on drugs for covid-19. bmj 2020;370

59. Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. Journal of clinical epidemiology 2013;66(7):726-35 Pubmed Journal

60. World Health Organization. Criteria for releasing COVID-19 patients from isolation. Scientific brief. 2020. Website

61. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. The New England journal of medicine 2020;382(22):2081-2090 Pubmed Journal

62. World Health Organization. Dengue guidelines, for diagnosis, treatment, prevention and control. 2009. Website

63. World Health Organization. Infection prevention and control for long-term care facilities in the context of COVID-19. 2020. Website

64. Moons KGM, Wolff RF, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration. Annals of internal medicine 2019;170(1):W1-W33 Pubmed Journal

65. Chen N., Zhou M., Dong X., Qu J., Gong F., Han Y., et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507-513 Pubmed Journal Website

66. Guan WJ, Ni ZY, Hu Y., Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382(18):1708-1720 Pubmed Journal Website

67. Tong JY, Wong A., Zhu D., Fastenberg JH, Tham T.. The Prevalence of Olfactory and Gustatory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis. Otolaryngol Head Neck Surg 2020;194599820926473 Pubmed Journal Website

68. Elshafeey F, Magdi R, Hindi N, Elshebiny M, Farrag N, Mahdy S, et al. A systematic scoping review of COVID-19 during pregnancy and childbirth. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2020;150(1):47-52 Pubmed Journal

69. . Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020. MMWR. Morbidity and mortality weekly report 2020;69(14):422-426 Pubmed Journal

70. Evans LE, Rhodes A, Alhazzani W, Antonelli M, Coopersmith C, French CJ, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47(11):1181-1247. Pubmed Journal Website

71. Yan G., Lee CK, Lam LTM, Yan B., Chua YX, Lim AYN, et al. Covert COVID-19 and false-positive dengue serology in Singapore. Lancet Infect Dis 2020. Pubmed Journal Website

72. World Health Organization. Home care for patients with COVID-19 presenting with mild symptoms and management of their contacts: interim guidance, 17 March 2020. World Health Organization 2020.

73. Duncan H., Hutchison J., Parshuram CS. The Pediatric Early Warning System score: a severity of illness score to predict urgent medical need in hospitalized children. J Crit Care 2006;21(3):271-8 Pubmed Journal Website

74. Teng X-B, Shen YA, Han M-F, Yang G, Zha L, Shi J-F. The value of high-flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia. European journal of clinical investigation 2021;51(3):e13435 Pubmed Journal

75. Li MK. Effect of transnasal high-flow humidifying oxygen therapy for the treatment of new coronavirus pneumonia with acute respiratory failure. Chinese Journal of Coal Industry Medicine 2020;23:221-224

76. Detsky ME, Jivraj N., Adhikari NK, Friedrich JO, Pinto R., Simel DL, et al. Will This Patient Be Difficult to Intubate?: The Rational Clinical Examination Systematic Review. JAMA 321(5):493-503 Pubmed Journal Website

77. Guerin C., Reignier J., Richard JC, Beuret P., Gacouin A., Boulain T., et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368(23):2159-68 Pubmed Journal Website

78. Messerole E., Peine P., Wittkopp S., Marini JJ, Albert RK. The pragmatics of prone positioning. Am J Respir Crit Care Med 2002;165(10):1359-63 Pubmed Journal Website

79. Briel M., Meade M., Mercat A., Brower RG, Talmor D., Walter SD, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA 303(9):865-73 Pubmed Journal Website

80. Goligher EC, Kavanagh BP, Rubenfeld GD, Adhikari NK, Pinto R., Fan E., et al. Oxygenation response to positive end-expiratory pressure predicts mortality in acute respiratory distress syndrome. A secondary analysis of the LOVS and ExPress trials. Am J Respir Crit Care Med 2014;190(1):70-6 Pubmed Journal Website

81. Felten-Barentsz K, van Oorsouw R, Klooster E, Koenders N, Driehuis F, Hulzebos EH, et al. Recommendations for hospital-based physical therapists managing patients with COVID-19. Physical Therapy 2020;100(9):1444-1457 Journal

82. Munshi L., Walkey A., Goligher E., Pham T., Uleryk EM, Fan E.. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. Lancet Respir Med 2019;7(2):163-172 Pubmed Journal Website

83. World Health Organization. Pocket book of hospital care for children: Guidelines for the management of common childhood illnesses: Second edition. 2020. Website

84. Bridwell RE, Carius BM, Long B, Oliver JJ, Schmitz G. Sepsis in Pregnancy: Recognition and Resuscitation. The western journal of emergency medicine 2019;20(5):822-832 Pubmed Journal

85. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Critical care medicine 2018;46(9):e825-e873 Pubmed Journal

86. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2011;52(9):e162-93 Pubmed Journal

87. Muscedere J, Dodek P, Keenan S, Fowler R, Cook D, Heyland D, et al. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: prevention. Journal of critical care 2008;23(1):126-37 Pubmed Journal

88. Schmidt GA, Girard TD, Kress JP, Morris PE, Ouellette DR, Alhazzani W, et al. Official Executive Summary of an American Thoracic Society/American College of Chest Physicians Clinical Practice Guideline: Liberation from Mechanical Ventilation in Critically Ill Adults. American journal of respiratory and critical care medicine 2017;195(1):115-119 Pubmed Journal

89. McArdle AJ, Vito O, Patel H, Seaby EG, Shah P, Wilson C, et al. Treatment of Multisystem Inflammatory Syndrome in Children. N Engl J Med 2021;385(1):11-22 Journal Website

90. Ouldali N, Toubiana J, Antona D, Javouhey E, Madhi F, Lorrot M, et al. Association of Intravenous Immunoglobulins Plus Methylprednisolone vs Immunoglobulins Alone With Course of Fever in Multisystem Inflammatory Syndrome in Children. JAMA 2021;325(9):855-864 Journal Website

91. Thompson EJ, Williams DM, Walker AJ, Mitchell RE, Niedzwiedz CL, Yang TC, et al. Risk factors for long COVID: analyses of 10 longitudinal studies and electronic health records in the UK. medRxiv 2021;2021.06.24.21259277 Journal Website

92. Volkow ND. Collision of the COVID-19 and addiction epidemics. Annals of Internal Medicine 2020;173(1):61-62 Journal

93. Taquet M., Geddes JR, Husain M., Luciano S., Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry 2021;8(5):416-427 Pubmed Journal

94. Ostuzzi G, Gastaldon C, Papola D, Fagiolini A, Dursun S, Taylor D, et al. Pharmacological treatment of hyperactive delirium in people with COVID-19: rethinking conventional approaches. Ther Adv Psychopharmacol 2020;10:1-9 Journal

95. World Health Organization. Doing what matters in times of stress. An illustrated guide. Website

96. Michelen M, Manoharan L, Elkheir N, Cheng V, Dagens D, Hastie C. Characterising long-term covid-19: a rapid living systematic review. medRxiv. Published online December 9:2020-12

97. Mehra MR, Desai SS, Kuy S., Henry TD, Patel AN. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med 2020. Pubmed Journal Website

98. Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. JAMA network open 2021;4(5):e2111417-e2111417

99. Huang M., Parker AM, Bienvenu OJ, Dinglas VD, Colantuoni E., Hopkins RO, et al. Psychiatric Symptoms in Acute Respiratory Distress Syndrome Survivors: A 1-Year National Multicenter Study. Crit Care Med 2016;44(5):954-65 Pubmed Journal Website

100. Van Aerde N, Van den Berghe G, Wilmer A, Gosselink R, Hermans G, COVID-19 Consortium. Intensive care unit acquired muscle weakness in COVID-19 patients. 2020;46(11):2083-2085 Journal

101. World Health Organization. Coronavirus disease - Answers. (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/coronavirus-disease-answers?query=variants+of+concern&referrerPageUrl=https%3A%2F%2Fwww.who.int%2Femergencies%2Fdiseases%2Fnovel-coronavirus-2019%2Fcoronavirus-disease-answers, accessed 02 November 2021) Website

102. Hart JL, Turnbull AE, Oppenheim IM, Courtright KR. Family-centered care during the COVID-19 era. J Pain Symptom Manage 2020;60(2):e93-e97 Journal

103. Buchan SA, Tibebu S, Daneman N, Whelan M, Vanniyasingam T, Murti M, et al. Increased household secondary attacks rates with Variant of Concern SARS-CoV-2 index cases. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2021. Pubmed Journal

104. Brodsky MB, Nollet JL, Spronk PE, Gonzalez-Fernandez M. Prevalence, pathophysiology, diagnostic modalities and treatment options for dysphagia in critically ill patients. American Journal of Physical Medicine & Rehabilitation 2020;99(12):1164-1170 Journal

105. Tegally H, Wilkinson E, Giovanetti M, Iranzadeh A, Fonseca V, Giandhari J, et al. Detection of a SARS-CoV-2 variant of concern in South Africa. Nature 2021;592(7854):438-443 Pubmed Journal

106. Greenhalgh T, Javid B, Knight M, Inada-Kim M. What is the efficacy and safety of rapid exercise tests for exertion desaturation in covid-19. Website

107. Sinha S, Tam B, Wang SM. Altered interaction between RBD and ACE2 receptor contributes towards the increased transmissibility of SARS CoV-2 delta, kappa, beta, and gamma strains with RBD double mutations. bioRxiv 2021. Journal Website

108. Metzl JD, McElheny K, Robinson JN, Scott DA, Sutton KM, Toresdahl BG. Considerations for return to exercise following mild-to-moderate COVID-19 in the recreational athlete. HSS J 2020;16(Suppl 1):1-6 Journal

109. Curran J, Dol J, Boulos L, Somerville M, McCulloch H, MacDonald M, et al. Transmission characteristics of SARS-CoV-2 variants of concern Rapid Scoping Review. medRxiv 2021. Journal Website

110. Phelan D, Kim JH, Chung EH. A Game Plan for the resumption of sport and exercise after Coronavirus Disease 2019 (COVID-19) Infection. JAMA Cardiol 2020. Journal

111. Campbell F, Archer B, Laurenson-Schafer H, Jinnai Y, Konings F, Batra N, et al. Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin 2021;26(24) Pubmed Journal

112. Belsher BE, Beech E, Evatt D, Smolenski DJ, Shea MT, Otto JL, et al. Present-centered therapy (PCT) for post-traumatic stress disorder (PTSD) in adults. Cochrane Database Syst Rev 2019;(11):CD012898 Journal

113. World Health Organization. WHO Consolidated Guideline on Self-Care Interventions for Health Sexual and Reproductive Health and Rights. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/bitstream/handle/10665/325480/9789241550550-eng.pdf?ua=1, accessed August 2022). Website

114. Severity of disease associated with Omicron variant as compared with Delta variant in hospitalized patients with suspected or confirmed SARS-CoV-2 infection. Website

115. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr 2020;9(1):51-60 Pubmed Journal

116. World Health Organization. Preventing and managing COVID-19 across long-term care services: policy brief. 2020. Website

117. World Health Organization. Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus (MERS-CoV) infection is suspected: interim guidance. World Health Organization 2019.

118. Wang H, Li T, Barbarino P, Gauthier S, Broadly H, Molinuevo JL, et al. Dementia care during COVID-19. Lancet 2020;395(10231):1190-1191 Journal

119. Wang H. Delirium: a suggestive sign of COVID-19 in dementia. EClinicalMedicine 2020;100524 Journal

120. World Health Organization. Therapeutics and COVID-19: living guideline, 24 September 2021. World Health Organization 2021.

121. World Health Organization. Mental health of older adults. Key facts. Geneva. World Health Organization. 2017. (https://www.who.int/news-room/fact-sheets/detail/mental-health-of-older-adults accessed 13 May 2020). 2017. Website

122. Albutt K, Luckhurst CM, Alba GA, Hechi ME, Mokhati A, Breen K, et al. Design and Impact of a COVID-19 Multidisciplinary Bundled Procedure Team. Ann Surg 2020;272(2):e72-e73 Journal

123. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed.) 2008;336(7650):924-6 Pubmed Journal

124. Mahler DA, Selecky PA, Harrod CG, Benditt JO, Carrieri-Kohlman V., Curtis JR, et al. American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease. Chest 2010;137(3):674-91 Pubmed Journal Website

125. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. BMJ (Clinical research ed.) 2008;336(7652):1049-51 Pubmed Journal

126. Andrenelli E, Negrini F, De Sire A, Patrini M, Lazzarini SG, Ceravolo MG, et al. Rehabilitation and COVID-19: a rapid living systematic review 2020 by Cochrane Rehabilitation Field. Update as of September 30th, 2020. European journal of physical and

rehabilitation medicine 2020. Pubmed Journal

127. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of clinical epidemiology 2011;64(4):401-6 Pubmed Journal

128. Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. BMJ 2021;372:n136 Journal Website

129. Goodacre S, Thomas B, Lee E, Sutton L, Loban A, Waterhouse S, et al. Post-exertion oxygen saturation as a prognostic factor for adverse outcome in patients attending the emergency department with suspected COVID-19: a substudy of the PRIEST observational cohort study. Emerg Med J 38(2):88-93 Journal Website

130. Recommendations for national SARS-CoV-2 testing strategies and diagnostic capacities. Website

131. Greenhalgh T, Javid B, Knight M, Inada-Kim M. What is the efficacy and safety of rapid exercise tests for exertional desaturation in covid-19?. Centre for Evidence-Based Medicine (https://www.cebm.net/covid-19/what-is-the-efficacy-and-safety-of-rapid-exercise-tests-for-exertional-desaturation-in-covid-19/, accessed August 2022). Website

132. Infection prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed. Website

133. Núñez-Cortés R, Rivera-Lillo G, Arias-Campoverde M, Soto-García D, García-Palomera R, Torres-Castro R. Use of sit-to-stand test to assess the physical capacity and exertional desaturation in patients post COVID-19. Chron Respir Dis 2021;18 Journal Website

134. The COVID-19 Clinical Care Pathway. Website

135. Paling C. The complex problem of identifying serious pathology in Musculoskeletal care: Managing clinical risk during the COVID pandemic and beyond. Musculoskeletal Science and Practice 2021;54:102379. Journal Website

136. Paterson I, Ramanathan K, Aurora R, Bewick D, Chow C-M, Clarke B, et al. Long COVID-19: A Primer for Cardiovascular Health Professionals, on Behalf of the CCS Rapid Response Team. Can J Cardiol 2021;37(8):1260-1262 Journal Website

137. World Health Organization. Infection, prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed (Interim Guidance). 2020. Website

138. Ahmad M, Kim K, Indorato D, Petrenko I, Diaz K, Rotatori F, et al. Post-COVID Care Center to Address Rehabilitation Needs in COVID-19 Survivors: A Model of Care. American Journal of Medical Quality 2021;37(3):266--271

139. World Health Organization. Mask use in the context of COVID-19. Interim guidance. 2020. Website

140. Parkin A, Davison J, Tarrant R, Ross D, Halpin S, Simms A, et al. A Multidisciplinary NHS COVID-19 Service to Manage Post-COVID-19 Syndrome in the Community. J Prim Care Community Health 2021;12

141. COVID-19 rapid guideline: managing the long-term effects of COVID-19, NICE guideline [NG188]. Published: 18 December 2020 Last updated: 11 November 2021 (https://www.nice.org.uk/guidance/ng188, accessed August 2022). Website

142. McMichael TM, Currie DW, Clark S., Pogosjans S., Kay M., Schwartz NG, et al. Epidemiology of Covid-19 in a Long-Term Care Facility in King County, Washington. N Engl J Med 2020. Pubmed Journal Website

143. Albu S, Zozaya NR, Murillo N, García-Molina A, Chacón CAF, Kumru H. What's going on following acute covid-19? Clinical characteristics of patients in an out-patient rehabilitation program. NeuroRehabilitation 2021;48(4):469-480

144. Tay HS, Harwood R.. Atypical presentation of COVID-19 in a frail older person. Age Ageing 2020. Pubmed Journal Website

145. Ladds E, Rushforth A, Wieringa S, Taylor S, Rayner C, Husain L, et al. Persistent symptoms after Covid-19: qualitative study of 114 ``long Covid'' patients and draft quality principles for services. BMC Health Serv Res 2020;20(1)

146. World Health Organization. WHO consolidated guidelines on tuberculosis: Module 1: Prevention - infection prevention and control. 2022. Website

147. Santhosh L, Block B, Kim SY, Raju S, Shah RJ, Thakur N, et al. Rapid Design and Implementation of Post-COVID-19 Clinics. Chest 2021;160(2):671-677

148. World Health Organization. Guidelines for the treatment of malaria, 3rd edition. 2015. Website

149. Banić M, Janković Makek M, Samaržija M, Muršić D, Boras Z, Trkeš V, et al. Risk factors and severity of functional impairment in long COVID: a single-center experience in Croatia. Croat Med J 2022;63(1):27--35

150. National Institute for Health and Care Excellence. Myalgic Encephalomyelitis (or Encephalopathy) / Chronic Fatigue Syndrome: diagnosis and management. NICE Guideline 2021. Website

151. World Health Organization. WHO Information Note: COVID-19 considerations for tuberculosis (TB) care. 2021. Website

152. Stussman B, Williams A, Snow J, Gavin A, Scott R, Nath A, et al. Characterization of Post--exertional Malaise in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Front Neurol 2020;11

153. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 2: Screening - systematic screening for tuberculosis disease. 2021. Website

154. Vadlamudi N, Basham CA, Johnston J, Battista Migliori G, Centis R, D'Ambrosio L, et al. The Association of SARS-CoV-2 Infection and Tuberculosis Disease with Unfavorable Treatment Outcomes: A Systematic Review. Website

155. Chu L, Valencia IJ, Garvert DW, Montoya JG. Deconstructing post-exertional malaise in myalgic encephalomyelitis/ chronic fatigue syndrome: A patient-centered, cross-sectional survey. PLoS One 2018;13(6):e0197811

156. Brown DA, O'Brien KK. Conceptualising Long COVID as an episodic health condition. BMJ Glob Health 2021;6(9):e007004

157. World Health Organization. Community based health care including outreach and campaigns in the context of the COVID-19 pandemic Interim Guidance May 2020 WHO IFRC UNICEF. 2020. Website

158. O'Brien KK, Brown DA, Bergin C, Erlandson KM, Vera JH, Avery L, et al. Long COVID and episodic disability: advancing the conceptualisation, measurement and knowledge of episodic disability among people living with Long COVID -- protocol for a mixed-methods study. BMJ Open 2022;12(3):e060826

159. World Health Organization. WHO-ICRC Basic Emergency Care: approach to the acutely ill and injured. 2018. Website

160. National Institute of Neurological Disorders and Stroke. NINDS Common Data Elements (CDE) Group Post-Exertional Malaise Subgroup Summary - Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Journal Website

161. World Health Organization. Clinical care for severe acute respiratory infection: toolkit: COVID-19 adaptation. 2020. Website

162. Hønge BL, Hermansen M-LF, Storgaard M. Reactive arthritis after COVID-19. BMJ Case Rep 2021;14(3):e241375 Journal Website

163. Huang C., Wang Y., Li X., Ren L., Zhao J., Hu Y., et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506 Pubmed Journal Website

164. Hoong CWS, Amin MNME, Tan TC, Lee JE. Viral arthralgia a new manifestation of COVID-19 infection? A cohort study of COVID-19-associated musculoskeletal symptoms. Int J Infect Dis 2021;104:363-369 Journal Website

165. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ 370:m3320 Journal

166. Ono K, Kishimoto M, Shimasaki T, Uchida H, Kurai D, Deshpande GA, et al. Reactive arthritis after COVID-19 infection. RMD Open 2020;6:e001350. Journal Website

167. Wu Z., McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020. Pubmed Journal Website

168. Mokuda S, Tokunaga T, Masumoto J, Sugiyama E. Angiotensin-converting enzyme 2, a SARS-CoV-2 receptor, is upregulated by interleukin-6 via STAT3 signaling in rheumatoid synovium. J Rheumatol 2020. Journal Website

169. Yang X., Yu Y., Xu J., Shu H., Xia J., Liu H., et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020. Pubmed Journal Website

170. Taha SI, Samaan SF, Ibrahim RA, El-Sehsah EM, Youssef MK. Post-COVID-19 arthritis: is it hyperinflammation or autoimmunity?. Eur Cytokine Netw 2021;32(4):83-88 Journal Website

171. Gasparotto M., Framba V., Piovella C., Doria A., Iaccarino L. Post-COVID-19 arthritis: a case report and literature review. Clin Rheumatol 2021;40(8):3357-3362 Journal Website

172. Derksen VFAM, van der Woude D. Response to: 'Correspondence on 'Onset of rheumatoid arthritis after COVID-19: coincidence or connected?'' by Roongtaet al. Ann Rheum Dis 2021. Journal Website

173. Wang D., Hu B., Hu C., Zhu F., Liu X., Zhang J., et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020. Pubmed Journal Website

174. Baimukhamedov C, Barskova T, Matucci-Cerinic M. Arthritis after SARS-CoV-2 infection. Lancet Rheumatol 2021;3(5):e324-e325 Journal Website

175. Mimura T, Kondo Y, Ohta A, Iwamoto M, Ota A. Evidence-based clinical practice guideline for adult Still's disease. Mod Rheumatol 2018;28(5):736-757 Pubmed Journal

176. Giacomelli A., Pezzati L., Conti F., Bernacchia D., Siano M., Oreni L., et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis 2020. Pubmed Journal Website

177. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid—mechanisms, risk factors, and management. BMJ 2021;374:n1648 Journal Website

178. Ortelli P, Ferrazzoli D, Sebastianelli L, Engl M, Romanello R, Nardone REA. Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging symptom. J Neurol Sci 2021;420:117271

179. Cicerone KD, Goldin Y, Ganci K, Rosenbaum A, Wethe JV, Langenbahn DEA. Evidence-based cognitive rehabilitation: systematic review of the literature from 2009 through 2014. Arch Phys Med Rehabil 100(8):1515-1533

180. das Nair R, Cogger H, Worthington E, Lincoln NB. Cognitive rehabilitation for memory deficits after stroke. Cochrane Database Sys Rev 2016.(9)

181. Loetscher T, Potter KJ, Wong D, das Nair R. Cognitive rehabilitation for attention deficits following stroke. Cochrane Database Sys Rev 2019.(11)

182. Weiss SL, Peters MJ, Alhazzani W., Agus MSD, Flori HR, Inwald DP, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med 2020;46(Suppl 1):10-67 Pubmed Journal Website

183. Best W, Hughes LM, Masterson J, Thomas M, Fedor A, Roncoli SEA. Intervention for children with word-finding difficulties: a parallel group randomised control trial. Int J Speech Lang Pathol 2018;20(7):708-719

184. Antigen-detection in the diagnosis of SARS-CoV-2 infection. Website

185. Lee SY, Amatya B, Judson R, Truesdale M, Reinhardt JD, Uddin TEA. Clinical practice guidelines for rehabilitation in traumatic brain injury: a critical appraisal. Brain Int 2019;33(10):1263-1271

186. Use of SARS-CoV-2 antigen-detection rapid diagnostic tests for COVID-19 self-testing. 2022. Website

187. Bahar-Fuchs A, Martyr A, Goh AM, Sabates J, Clare L. Cognitive training for people with mild to moderate dementia. Cochrane Database Sys Rev 2019.(3)

188. World Health Organization. Diagnostic testing for SARS-CoV-2 interim guidance. 2020. Website

189. Vloothuis JD, Mulder M, Veerbeek JM, Konijnenbelt M, Visser-Meily JM, Ket JEA. Caregiver-mediated exercises for improving outcomes after stroke. Cochrane Database Sys Rev 2016.(12)

190. TH L, RJ L, RTP L, T B, al ET. Testing for SARS-CoV-2: Can we stop at 2?. Clinical Infectious diseases 2020;71(16):2246-2248 Journal

191. Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PloS one 2020;15(11):e0240784

192. World Health Organization. Rational use of personal protective equipment for coronavirus disease (COVID-19) and considerations during severe shortages. Interim guidance. 2020. Website

193. Handreiking ergotherapie bij COVID-19 clienten in de herstelfase. 2021.

194. World Health Organization. Transmission of SARS-CoV-2: implications for infection prevention precautions. Scientific brief. 2020. Website

195. Thomas P, Baldwin C, Beach L, Bissett B, Boden I, Cruz SM, et al. Physiotherapy management for COVID-19 in the acute hospital setting and beyond: an update to clinical practice recommendations. J Physiother 2022;68(1):8-25

196. Antigen-detection in the diagnosis of SARS-CoV-2 infection. 2021. Website

197. Kim S, Xu Y, Dore K, Gewurtz R, Larivière N, Letts L. Fatigue self-management led by occupational therapists and/or physiotherapists for chronic conditions: A systematic review and meta-analysis. Chronic Illn

198. Rawson TM, Moore LSP, Zhu N., Ranganathan N., Skolimowska K., Gilchrist M., et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis 2020. Pubmed Journal Website

199. Farragher JF, Ravani P, Manns B, Elliott M, Thomas C, Donald M, et al. A pilot randomised controlled trial of an energy management programme for adults on maintenance haemodialysis: the fatigue-HD study. BMJ open 2022;12(2):e051475

200. World Health Organization. Compendium of WHO malaria guidance – prevention, diagnosis, treatment, surveillance and elimination. 2019. Website

201. Hameed F, Palatulan E, Jaywant A, Said R, Lau C, Sood V, et al. Outcomes of a COVID-19 recovery program for patients hospitalized with SARS-CoV-2 infection in New York City: A prospective cohort study. PM&R 2021;13(6):609-617

202. Parker JK, Kelly CE, Smith BC, Kirkwood AF, Hopkins C, Gane S. Patients' perspectives on qualitative olfactory dysfunction: Thematic analysis of social media posts. JMIR Form Res 2021;5(12):e29086

203. World Health Organization. Readiness for influenza during the COVID-19 pandemic. (https://www.who.int/publications/i/item/WHO-2019-nCoV-Influenza-readiness-COVID-19-2020.1, accessed 17 January 2021) Website

204. Prem B, Liu DT, Besser G, Sharma G, Dultinger LE, Hofer SV, et al. Long-lasting olfactory dysfunction in COVID-19 patients. Eur Arch Otorhinolaryngol 2022;279(7):3485-3492

205. Pekala K, Chandra RK, Turner JH. Efficacy of olfactory training in patients with olfactory loss: a systematic review and meta-analysis. Int Forum Allergy Rhinol 6:299-307

206. World Health Organization. The use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19. 2020. Website

207. Hopkins C, Alanin M, Philpott C, Harries P, Whitcroft K, Qureishi A, et al. Management of new onset loss of sense of smell during the COVID-19 pandemic-BRS Consensus Guidelines. Clin Otolaryngol 2021;46(1):16-22

208. Greenhalgh T., Koh GCH, Car J.. Covid-19: a remote assessment in primary care. BMJ 2020;368:m1182 Pubmed Journal Website

209. Larsen NW, Stiles LE, Shaik R, Schneider L, Muppidi S, Tsui CEA. Characterization of Autonomic Symptom Burden in Long COVID: A Global Survey of 2,314 Adults. medRxiv 2022.

210. Goossens H., Ferech M., Vander Stichele R., Elseviers M., Group EP. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005;365(9459):579-87 Pubmed Journal Website

211. Wieling W, Van Dijk N, Thijs R, de Lange F, Krediet CP, Halliwill J. Physical countermeasures to increase orthostatic tolerance. J Gen Intern Med 2015;277(1):69-82

212. Llor C., Bjerrum L.. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. Ther Adv Drug Saf 2014;5(6):229-41 Pubmed Journal Website

213. Lahrmann H, Cortelli P, Hilz M, Mathias C, Struhal W, Tassinari M. EFNS guidelines on the diagnosis and management of orthostatic hypotension. Eur J Neurol 2006;13(9):930-936

214. World Health Organization. AWARE classification of antibiotics. 2019. Website

215. Fu Q, Levine BD. Exercise in the postural orthostatic tachycardia syndrome. Auton Neurosci 2015;188:86-89

216. Langford B. Antimicrobial Resistance in Patients with COVID-19: A Systematic Review and Meta-Analysis. Lancet Microbe Website

217. Cichero JA, Lam P, Steele CM, Hanson B, Chen J, Dantas REA. Development of international terminology and definitions for texture-modified foods and thickened fluids used in dysphagia management: the IDDSI framework. Dysphagia 2017;32(2):293-314

218. Steele CM, Namasivayam-MacDonald AM, Guida BT, Cichero JA, Duivestein J, Hanson BEA. Creation and initial validation of the international dysphagia diet standardisation initiative functional diet scale. Arch Phys Med Rehabil 2018;99(5):934-944

219. World Health Organization. Paediatric emergency triage, assessment and treatment. 2016. Website

220. Ohmae Y, Logemann JA, Hanson DG, Kaiser P, Kahrilas PJ. Effects of two breath-holding maneuvers on oropharyngeal swallow. Ann Otol Rhinol Laryngol 1996;105(2):123-131

221. Thomas P., Baldwin C., Bissett B., Boden I., Gosselink R., Granger CL, et al. Physiotherapy management for COVID-19 in the acute hospital setting: clinical practice recommendations. J Physiother 2020. Pubmed Journal Website

222. Fukuoka T, Ono T, Hori K, Tamine K-I, Nozaki S, Shimada KEA. Effect of the effortful swallow and the Mendelsohn maneuver on tongue pressure production against the hard palate. Dysphagia 2013;28(4):539-547

223. World Health Organization. Oxygen therapy for children: a manual for health workers. 2016. Website

224. Kahrilas P, Logemann J, Krugler C, Flanagan E. Volitional augmentation of upper esophageal sphincter opening during swallowing.

Am J Physiol Gastrointest Liver Physiol 1991;260(3):G450-G456

225. Schultz MJ, Dünser MW, Dondorp AM. Current Challenges in the Management of Sepsis in ICUs in Resource-Poor Settings and Suggestions for the Future. 2019. Pubmed Journal

226. Wheeler-Hegland KM, Rosenbek JC, Sapienza CM. Submental sEMG and hyoid movement during Mendelsohn maneuver, effortful swallow, and expiratory muscle strength training. J Speech Lang Hear Res 2008.

227. World Health Organization. Oxygen sources and distribution for COVID-19 treatment. 2020. Website

228. Steele CM, Alsanei WA, Ayanikalath S, Barbon CE, Chen J, Cichero JEA. The influence of food texture and liquid consistency modification on swallowing physiology and function: a systematic review. Dysphagia 2015;30(1):2-26

229. Andersen UT, Beck AM, Kjaersgaard A, Hansen T, Poulsen I. Systematic review and evidence based recommendations on texture modified foods and thickened fluids for adults (≥ 18 years) with oropharyngeal dysphagia. ESPEN J 8(4):e127-e134

230. Ospina-Tascón GA, Calderón-Tapia LE, García AF, Zarama V, Gómez-Álvarez F, Álvarez-Saa T, et al. Effect of High-Flow Oxygen Therapy vs Conventional Oxygen Therapy on Invasive Mechanical Ventilation and Clinical Recovery in Patients With Severe COVID-19: A Randomized Clinical Trial. JAMA 2021;326(21):2161-2171 Pubmed Journal

231. Kosztyła-Hojna B, Moskal-Jasińska D, Kraszewska A, Łobaczuk-Sitnik A, Zdrojkowski M, Duchnowska E, et al. Verbal communication disorders in psychogenic dysphonia. Otolaryngol Pol 2019;73:14-20

232. Saniasiaya J, Kulasegarah J, Narayanan P. New-onset dysphonia: a silent manifestation of COVID-19. Ear Nose Throat J 2021.

233. Perkins GD, Ji C, Connolly BA, Couper K, Lall R, Baillie JK, et al. An adaptive randomized controlled trial of non-invasive respiratory strategies in acute respiratory failure patients with COVID-19. medRxiv 2021. Journal Website

234. Speyer R. Effects of voice therapy: a systematic review. J Voice 2008;22(5):565-580

235. Grieco DL, Menga LS, Cesarano M, Rosà T, Spadaro S, Bitondo MM, et al. Effect of Helmet Noninvasive Ventilation vs High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure: The HENIVOT Randomized Clinical Trial. JAMA 2021;325(17):1731-1743 Pubmed Journal

236. Castillo-Allendes A, Contreras-Ruston F, Cantor-Cutiva LC, Codino J, Guzman M, Malebran C, et al. Voice therapy in the context of the COVID-19 pandemic: guidelines for clinical practice. J Voice 2021;35(5):717-727

237. Kelly SE, Wells GA. Noninvasive ventilation strategies for patients with severe or critical COVID-19: A rapid review of clinical outcomes. medRxiv 2022. Journal Website

238. Eastwood C, Madill C, Mccabe P. The behavioural treatment of muscle tension voice disorders: a systematic review. Int J Speech Lang Pathol 2015;17(3):287-303

239. Peng PWH, Ho PL, Hota SS. Outbreak of a new coronavirus: what anaesthetists should know. Br J Anaesth 2020;124(5):497-501 Pubmed Journal Website

240. Desjardins M, Halstead L, Cooke M, Bonilha HS. A systematic review of voice therapy: What “effectiveness” really implies. J Voice 31(3):392. e13-392. e32

241. Cheung JC, Ho LT, Cheng JV, Cham EYK, Lam KN. Staff safety during emergency airway management for COVID-19 in Hong Kong. Lancet Respir Med 2020;8(4):e19 Pubmed Journal Website

242. Yiu EM-L, Lo MC, Barrett EA. A systematic review of resonant voice therapy. Int J Speech Lang Pathol 19(1):17-29

243. da Cunha Pereira G, de Oliveira Lemos I, Gadenz CD, Cassol M. Effects of voice therapy on muscle tension dysphonia: a systematic

literature review. J Voice 2018;32(5):546-552

244. NIH NHLBI ARDS Clinical Network. Mechanical Ventilation Protocol Summary. 2008. Website

245. Burton K, Caine A, Macniven A, Porter S, Rayner C, Yarker J. COVID-19 return to work guide: for managers. 2021.

246. Rimensberger PC, Cheifetz IM, Pediatric Acute Lung Injury Consensus Conference G. Ventilatory support in children with pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med 2015;16(5 Suppl 1):S51-60 Pubmed Journal Website

247. World Health Organization. Managing ethical issues in infectious disease outbreaks. 2016. Website

248. World Health Organization. COVID-19: Operational guidance for maintaining essential health services during an outbreak March 2020. 2020. Website

249. The COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials. (https://covid-nma.com, accessed 15 January 2021). 2021. Website

250. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354(24):2564-75 Pubmed Journal Website

251. World Health Organization. Global COVID-19: clinical platform. 2020. Website

252. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. The New England journal of medicine 2004;351(4):327-36 Pubmed

253. Amato MB, Meade MO, Slutsky AS, Brochard L., Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372(8):747-55 Pubmed Journal Website

254. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial I, Cavalcanti AB, Suzumura EA, Laranjeira LN, Paisani DM, Damiani LP, et al. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. JAMA 2017;318(14):1335-1345 Pubmed Journal Website

255. Papazian L., Forel JM, Gacouin A., Penot-Ragon C., Perrin G., Loundou A., et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363(12):1107-16 Pubmed Journal Website

256. National Heart L, Blood Institute PCTN, Moss M., Huang DT, Brower RG, Ferguson ND, et al. Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome. N Engl J Med 2019;380(21):1997-2008 Pubmed Journal Website

257. M V, M L, E G, P F, F D, S G, et al. Italian suggestions for pulmonary rehabilitation in COVID-19 patients recovering from acute respiratory failure: results of a Delphi process. Monaldi Arch Chest Dis 2020;90(2) Journal

258. Combes A., Hajage D., Capellier G., Demoule A., Lavoue S., Guervilly C., et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. N Engl J Med 2018;378(21):1965-1975 Pubmed Journal Website

259. Goligher EC, Tomlinson G, Hajage D, Wijeysundera DN, Fan E, Jüni P, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome and Posterior Probability of Mortality Benefit in a Post Hoc Bayesian Analysis of a Randomized Clinical Trial. JAMA 2018;320(21):2251-2259 Pubmed Journal

260. Arabi YM, Arifi AA, Balkhy HH, Najm H., Aldawood AS, Ghabashi A., et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. Ann Intern Med 2014;160(6):389-97 Pubmed Journal Website

261. Combes A., Brodie D., Bartlett R., Brochard L., Brower R., Conrad S., et al. Position paper for the organization of extracorporeal membrane oxygenation programs for acute respiratory failure in adult patients. Am J Respir Crit Care Med 2014;190(5):488-96 Pubmed

Journal Website

262. Andrews B, Semler MW, Muchemwa L, Kelly P, Lakhi S, Heimburger DC, et al. Effect of an Early Resuscitation Protocol on In-hospital Mortality Among Adults With Sepsis and Hypotension: A Randomized Clinical Trial. JAMA 2017;318(13):1233-1240 Pubmed Journal

263. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, et al. Mortality after fluid bolus in African children with severe infection. The New England journal of medicine 2011;364(26):2483-95 Pubmed Journal

264. Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. Annals of internal medicine 161(5):347-55 Pubmed Journal

265. Loubani OM, Green RS. A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheters and central venous catheters. Journal of critical care 30(3):653.e9-17 Pubmed Journal

266. Lamontagne F, Richards-Belle A, Thomas K, Harrison DA, Sadique MZ, Grieve RD, et al. Effect of Reduced Exposure to Vasopressors on 90-Day Mortality in Older Critically Ill Patients With Vasodilatory Hypotension: A Randomized Clinical Trial. JAMA 2020. Pubmed Journal

267. Klompas M, Branson R, Eichenwald EC, Greene LR, Howell MD, Lee G, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infection control and hospital epidemiology 2014;35 Suppl 2:S133-54 Pubmed

268. Klompas M, Li L, Kleinman K, Szumita PM, Massaro AF. Associations Between Ventilator Bundle Components and Outcomes. JAMA internal medicine 2016;176(9):1277-83 Pubmed Journal

269. Violi F., Pastori D., Cangemi R., Pignatelli P., Loffredo L.. Hypercoagulation and Antithrombotic Treatment in Coronavirus 2019: A New Challenge. Thromb Haemost 2020. Pubmed Journal Website

270. Siddamreddy S., Thotakura R., Dandu V., Kanuru S., Meegada S.. Corona Virus Disease 2019 (COVID-19) Presenting as Acute ST Elevation Myocardial Infarction. Cureus 2020;12(4):e7782 Pubmed Journal Website

271. Wichmann D., Sperhake JP, Lutgehetmann M., Steurer S., Edler C., Heinemann A., et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. Ann Intern Med 2020. Pubmed Journal Website

272. Marschall J, Mermel LA, Fakih M, Hadaway L, Kallen A, O'Grady NP, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals: 2014 update. Infection control and hospital epidemiology 2014;35(7):753-71 Pubmed Journal

273. Kotfis K., Williams Roberson S., Wilson JE, Dabrowski W., Pun BT, Ely EW. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. Crit Care 2020;24(1):176 Pubmed Journal Website

274. Struelens MJ. The epidemiology of antimicrobial resistance in hospital acquired infections: problems and possible solutions. BMJ 1998;317(7159):652-4 Pubmed Journal Website

275. Son MBF, Murray N, Friedman K, Young CC, Newhams MM, Feldstein LR, et al. Multisystem Inflammatory Syndrome in Children — Initial Therapy and Outcomes. N Engl J Med 2021;385(1):23-34 Journal Website

276. Vazzana N., Dipaola F., Ognibene S.. Procalcitonin and secondary bacterial infections in COVID-19: association with disease severity and outcomes. Acta Clin Belg 2022;77(2):268-272 Pubmed Journal

277. Vanhomwegen C, Veliziotis I, Malinverni S, Konopnicki D, Dechamps P, Claus M, et al. Procalcitonin accurately predicts mortality but not bacterial infection in COVID-19 patients admitted to intensive care unit. Irish journal of medical science 2021;190(4):1649-1652 Pubmed Journal

278. Bertagnolio S, Thwin SS, Silva R, Nagarajan S, Jassat W, Fowler R, et al. Clinical features of, and risk factors for, severe or fatal COVID-19 among people living with HIV admitted to hospital: analysis of data from the WHO Global Clinical Platform of COVID-19. The Lancet HIV 2022. Journal Website

279. Beaud V, Crottaz-Herbette S, Dunet V, Vaucher J, Bernard-Valnet R, Du Pasquier R, et al. Pattern of cognitive deficits in severe COVID-19. Journal of neurology, neurosurgery and psychiatry 2020;jnnp-2020-325173 Journal

280. Wang Q, Xu R, Volkow ND. Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States. World Psychiatry 2020;7:10.1002/wps.20806 Journal

281. Li L, Li F, Fortunati F, Krystal JH. Association of a Prior Psychiatric Diagnosis with mortality among hospitalised patients with coronavirus disease 2019 (COVID-19) Infection. JAMA Netw Open 2020;3(9):e2023282 Journal

282. Bianchetti A, Rozzini R, Guerini F, Boffelli S, Ranieri P, Minelli G, et al. Clinical Presentation of COVID-19 in dementia patients. The journal of Nutrition, health & aging 2020;24(6):560-562 Journal

283. Hwang JM, Kim JH, Park JS, Chang MC, Park D. Neurological diseases as mortality predictive factors for patients with COVID-19: a retrospective cohort study. Neurological sciences 2020;41(9):2317-2324 Journal

284. Woolf S, Chapman DA, Sabo RT, Weinberger DM, Hill L. Excess deaths from COVID-19 and other causes March-April 2020. JAMA 2020;324(5):510-513 Journal

285. Bourne RS, Mills GH. Sleep disruption in critically ill patients--pharmacological considerations. Anaesthesia 2004;59(4):374-84 Pubmed Journal Website

286. Barr J., Fraser GL, Puntillo K., Ely EW, Gelinas C., Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41(1):263-306 Pubmed Journal Website

287. Huang J-A, Chen W-H, Liao N-C, Wu CL, Fu Y-C, Chen P-L. Acute delirium as an initial manifestation of COVID-19 patients with acute ischemic stroke: Report on two cases. J Formos Med Assoc 2022. Pubmed Website

288. Antoniello D., Milstein MJ, Dardick J., Fernandez-Torres J., Lu J., Patel N., et al. Altered mental status in COVID-19. J Neurol 2022;269(1):12-18 Pubmed Journal

289. Ostuzzi G, Papola D, Gastaldon C, Schoretsanitis G, Bertolini F, Amaddeo F, et al. Safety of psychotropic medications in people with COVID-19: evidence review and practical recommendations. BMC Med 2020;18(1):215 Journal

290. World Health Organization. Interim Briefing Note Addressing Mental Health and Psychosocial Aspects of COVID-19 Outbreak (developed by the IASC's Reference Group on Mental Health and Psychosocial Support). 2020. Website

291. World Health Organization. Basic Psychosocial skills: A guide for COVID-19 responders. 2020. Website

292. World Health Organization. mhGAP Evidence Resource Center: Support based on psychological first aid principles in people recently exposed to a traumatic event. 2012. Website

293. World Health Organization. Psychological first aid: Guide for field workers. 2012. Website

294. World Health Organization. mhGAP Evidence Resource Center: Evidence-based recommendations for management of depression in non-specialized health settings. 2012. Website

295. World Health Organization. mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings, version 2.0. 2016. Website

296. World Health Organization. COVID-19 and the use of angiotensin-converting enzyme inhibitors and receptor blockers. Scientific Brief. 2020. Website

297. Bauer A, Schreinlechner M, Sappler N, Dolejsi T, Tilg H, Aulinger BA, et al. Discontinuation versus continuation of renin-angiotensin-system inhibitors in COVID-19 (ACEI-COVID): a prospective, parallel group, randomised, controlled, open-label trial. The Lancet Respiratory Medicine 2021;9(8):863-872 Journal Website

298. Brodsky MB, Huang M., Shanholtz C., Mendez-Tellez PA, Palmer JB, Colantuoni E., et al. Recovery from Dysphagia Symptoms after Oral Endotracheal Intubation in Acute Respiratory Distress Syndrome Survivors. A 5-Year Longitudinal Study. Ann Am Thorac Soc 2017;14(3):376-383 Pubmed Journal Website

299. Mikkelsen ME, Shull WH, Biester RC, Taichman DB, Lynch S., Demissie E., et al. Cognitive, mood and quality of life impairments in a select population of ARDS survivors. Respirology 2009;14(1):76-82 Pubmed Journal Website

300. Dijkstra-Kersten SMA, Kok L., Kerckhoffs MC, Cremer OL, de Lange DW, van Dijk D., et al. Neuropsychiatric outcome in subgroups of Intensive Care Unit survivors: Implications for after-care. J Crit Care 2020;55:171-176 Pubmed Journal Website

301. Oeyen SG, Vandijck DM, Benoit DD, Annemans L., Decruyenaere JM. Quality of life after intensive care: a systematic review of the literature. Crit Care Med 38(12):2386-400 Pubmed Journal Website

302. Needham DM, Feldman DR, Kho ME. The functional costs of ICU survivorship. Collaborating to improve post-ICU disability. Am J Respir Crit Care Med 2011;183(8):962-4 Pubmed Journal Website

303. Cuthbertson BH, Roughton S., Jenkinson D., Maclennan G., Vale L.. Quality of life in the five years after intensive care: a cohort study. Crit Care 2010;14(1):R6 Pubmed Journal Website

304. Pfoh ER, Wozniak AW, Colantuoni E., Dinglas VD, Mendez-Tellez PA, Shanholtz C., et al. Physical declines occurring after hospital discharge in ARDS survivors: a 5-year longitudinal study. Intensive Care Med 2016;42(10):1557-1566 Pubmed Journal Website

305. Pandharipande PP, Girard TD, Jackson JC, Morandi A., Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med 2013;369(14):1306-16 Pubmed Journal Website

306. Hopkins RO, Weaver LK, Collingridge D., Parkinson RB, Chan KJ, Orme JFJ. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. Am J Respir Crit Care Med 2005;171(4):340-7 Pubmed Journal Website

307. Herridge MS, Tansey CM, Matte A., Tomlinson G., Diaz-Granados N., Cooper A., et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 2011;364(14):1293-304 Pubmed Journal Website

308. Dinglas VD, Aronson Friedman L, Colantuoni E, Mendez-Tellez PA, Shanholtz CB, Ciesla ND, et al. Muscle Weakness and 5-Year Survival in Acute Respiratory Distress Syndrome Survivors. Critical care medicine 2017;45(3):446-453 Pubmed Journal

309. Jaffri A, Jaffri UA. Post-Intensive care syndrome and COVID-19: crisis after crisis?. Heart Lung 2020;49(6):883-884 Journal

310. Herridge MS, Moss M, Hough CL, Hopkins RO, Rice TW, Bienvenu OJ, et al. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. Care Medicine 2016;42(5):725-738 Journal

311. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. New England Journal of Medicine 2003;348(8):683-93 Journal

312. Ong KC, Wei-Keong Ng A, Soon-U Lee L, Kaw G, Kwek SK, Khee-Shing Leow M, et al. 1-year pulmonary function and health status in survivors of severe acute respiratory syndrome. Chest 2005;128(3):1393-400 Journal

313. Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. Jourdan of medical virology 2020. Journal

314. Carfi A, Bernabei R, Landi F, Gemelli against COVID-19 Post-acute care study group. Persistent Symptoms in patients after acute COVID-19. JAMA 2020;324(6):603-605 Journal

315. Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome;a case-controlled study. BMC Neurology 2011;11:37 Journal

316. Dennis A, Wamil M, Kapur S, Alberts J, Badley AD, Decker GA, et al. Multi-organ impairment in low-risk individuals with long COVID. MedRxiv 2020. Journal

317. MW T, SS K, CJ L, EB R, NI S, al ET. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistage health care systems network-United States, March-June 2020. MMWR.Morbidity and Mortality Weekly Report 2020;69(30):993-998 Journal

318. Vaes AW, Machado FVC, Meys R, Delbressine JM, Goertz YMJ, Van Herck M, et al. Care dependency in non-hospitalized patients with COVID-19. Journal of clinical medicine 2020;9(9):2946 Journal

319. Chartered Society of Physiotherapy. Rehabilitation of adults who are hospitalised due to COVID-19: physiotherapy service delivery. 2020. Website

320. Leochico CFD. Adoption of tele rehabilitation in a developing country before and during the COVID-19 pandemic. Annals of Physical and Rehabilitation Medicine 2020;63(6):563-564 Journal

321. Johnson JK, Lapin B, Free K, Stilphen M. Frequency of physical therapist intervention is associated with mobility status and disposition at hospital discharge for patients with COVID-19. Physical Therapy 2020;pzaa181 Journal

322. Spruit MA, Holland AE, Singh SJ, Tonia T, Wilson KC, Troosters T. COVID-19: Interim guidance on rehabilitation in the hospital and post-hospital phase from a European Respiratory Society and American Thoracic Society-coordinated International Task Force. The European respiratory journal 2020;56(6):2002197 Journal

323. Barker-Davies RM, O´Sullivan O, Senaratne KPP, Baker P, Cranley M, harm-Datta S, et al. The Stanford Hall consensus statement for post COVID-19 rehabilitation. Br J Sports Med 2020;54(16):949-959 Journal

324. Hanquet G, Benahmed N, Castanares-Zapatero D. COVID-19- KCE contributors. Post intensive care syndrome in the aftermath of COVID-19: appendices. 2020. Website

325. Bolton CE, Bevan-Smith EF, Blakey JD. British Thoracic Society guideline on pulmonary rehabilitation in adults: accredited by NICE. Thorax 2013;68:ii1-ii30. Website

326. Royal Dutch Society for Physical Therapy (KNGF). KNGF position statement: Recommendations for physiotherapy in patients with COVID-19, July 2020.

327. Lewis C, Roberts NP, Bethell A, Robertson L, Bisson JI. Internet-based cognitive and behavioural therapies for post-traumatic stress disorder (PTSD) in adults. Cochrane Database Syst Rev 2018;12(12):CD11710 Journal

328. Allotey J, Chatterjee S, Kew T, Gaetano A, Stallings E, Fernández-García S, et al. SARS-CoV-2 positivity in offspring and timing of mother-to-child transmission: living systematic review and meta-analysis. BMJ 2022;376:e067696 Journal Website

329. World Health Organization. Recommendations on digital interventions for health system strengthening. Geneva: World Health Organization; 2019 (http://apps.who.int/iris/bitstream/handle/10665/311941/9789241550505-eng.pdf?ua=1, accessed August 2022). Website

330. World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization; 2016 (https://www.who.int/publications/i/item/9789241549912, accessed August 2022). Website

331. World Health Organization. Abortion care guideline. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/bitstream/handle/10665/277233/9789241550413-eng.pdf, accessed August 2022). Website

332. WHO Recommendations: Induction of labour at or beyond term. Geneva: World Health Organization; 2018 (https://apps.who.int/iris/bitstream/handle/10665/277233/9789241550413-eng.pdf, accessed August 2022). Website

333. WHO recommendations: Intrapartum care for a positive childbirth experience. Geneva: World Health Organization; 2018 (https://www.who.int/publications/i/item/9789241550215, accessed August 2022). Website

334. Buonsenso D, Costa S, Sanguinetti M, Cattani P, Posteraro B, Marchetti S, et al. Neonatal Late Onset Infection with Severe Acute Respiratory Syndrome Coronavirus 2. Am J Perinatol 2020;37(8):869-872 Pubmed Journal

335. Cui Y, Tian M, Huang D, Wang X, Huang Y, Fan LI, et al. A 55-Day-Old Female Infant Infected With 2019 Novel Coronavirus Disease: Presenting With Pneumonia, Liver Injury, and Heart Damage. J Infect Dis 2020;221(11):1775-1781 Pubmed Journal

336. Dong L, Tian J, He S, Zhu C, Wang J, Liu C, et al. Possible Vertical Transmission of SARS-CoV-2 From an Infected Mother to Her Newborn. JAMA 2020;323(18):1846-1848 Pubmed Journal

337. Fan C, Lei DI, Fang C, Li C, Wang M, Liu Y, et al. Perinatal Transmission of COVID-19 Associated SARS-CoV-2: Should We Worry?. Clin Infect Dis 2020. Pubmed Journal

338. Ferrazzi E, Frigerio L, Savasi V, Vergani P, Prefumo F, Barresi S, et al. Vaginal delivery in SARS-CoV-2-infected pregnant women in Northern Italy: a retrospective analysis. BJOG: Int J Obstet Gynaecol 2020;127(9):1116-1121 Pubmed Journal

339. Seo G, Lee G, Kim MJ, Baek S-H, Choi M, Ku KB, et al. Rapid Detection of COVID-19 Causative Virus (SARS-CoV-2) in Human Nasopharyngeal Swab Specimens Using Field-Effect Transistor-Based Biosensor. ACS nano 2020;14(4):5135-5142 Pubmed Journal

340. Kam K-Q, Yung CF, Cui L, Tzer Pin Lin R, Mak TM, Maiwald M, et al. A Well Infant With Coronavirus Disease 2019 With High Viral Load. Clin Infect Dis 2020;71(15):847-849 Pubmed Journal

341. Li Y, Zhao R, Zheng S, Chen XU, Wang J, Sheng X, et al. Lack of Vertical Transmission of Severe Acute Respiratory Syndrome Coronavirus 2, China. Emerg Infect Dis 2020;26(6):1335-1336 Pubmed Journal

342. Wang S, Guo L, Chen L, Liu W, Cao Y, Zhang J, et al. A Case Report of Neonatal 2019 Coronavirus Disease in China. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2020;71(15):853-857 Pubmed Journal

343. World Health Organization. WHO Essential newborn care and breastfeeding. 2002 (https://apps.who.int/iris/bitstream/handle/10665/107481/e79227.pdf, accessed August 2022). Website

344. Laosa O, Pedraza L, Alvarez-Bustos A, Carnicero JA, Rodriguez-Artalejo F, Rodriguez-Mañas L. Assessment at hospital admission of mortality risk from COVID-19: the role of functional status. Journal of the Medical Directors Association 2020;21(12) Journal

345. Petermann-Rocha F, Hanlon P, Gray SR, Welsh P, Gill JMR, Foster H. Comparison of two different frailty measurements and risk of hospitalisation or death from COVID-19: findings from UK Biobank. BMC Med 2020;18(1):355 Journal

346. Chinnadurai R, Ogedengbe O, Agarwal P, Money-Coomes S, Abdurrahman AZ, Mohammed S, et al. Older age and frailty are the chief predictors of mortality in COVID-19 patients admitted to an acute medical unit in a secondary care setting-a cohort study. BMC Geriatrics 2020;20(1):409 Journal

347. World Health Organization. Integrated care for older people (ICOPE): guidance for person-centred assessment and pathways in primary care. 2019. Website

348. Galluccio F, Ergonen T, A GM, AES A, M P-H, R A, et al. Treatment algorithm for COVID-19: a multidisciplinary point of view. Clinical Rheumatology 2020;39(7):2077-2084 Journal

349. Meisner BA, Boscart V, Gaudrenau P, Stolee P, Ebert P, Heyer M. Interdisciplinary and collaborative approaches needed to determine Impact of COVID-19 on older adults and aging: CAG/ACG and CJA/RCV joint statement. Canadian journal on aging 2020;39(3):333-343 Journal

350. Wang H, Li T, Gauthier S, Yu E, Tang Y, Barbarino P, et al. Coronavirus epidemic and geriatric mental healthcare in China: how a coordinated response by professional organisations helped older adults during an unprecedented crisis. International Psychogeriatrics 2020;32(10):1117-1120 Journal

351. World Health Organization. Disability considerations during the COVID-19 outbreak. 2020 (https://www.who.int/publications/i/item/9789241514460, accessed August 2022). Website

352. World Health Organization. WHO Guide Integrating palliative care and symptom relief into responses to humanitarian emergencies and crises. 2018 (https://www.who.int/publications/i/item/9789241514460, accessed August 2022). Website

353. Krakauer EL, Daubman BR, Aloudat T, Bhadelia N, Black L, Janjanin S, et al. Palliative care needs of people affected by natural hazards, political or ethnic conflict, epidemics of life-threatening infections, and other humanitarian crises. Waldman E, Glass M, (Eds.), A Field Manual for Palliative Care in Humanitarian Crises, New York: Oxford 2020;4-13

354. Greenhalgh T, Knight M, A´Court C, Buxton M, Husain L. Management of post-acute-covid-19 in primary care. BMJ 2020;370:m3026 Journal

355. Coppadoro A, Zago E, Pavan F, Foti G, Bellani G. The use of head helmets to deliver noninvasive ventilatory support: a comprehensive review of technical aspects and clinical findings. Crit Care 2021;25(1):327 Journal Website

356. Décary S, Dugas M, Stefan T, Langlois L, Skidmore B, Bhéreur A, et al. Care Models for Long COVID : A Rapid Systematic Review. medRxiv 2021. Journal Website

357. Postigo-Martin P, Cantarero-Villanueva I, Lista-Paz A, Castro-Martín E, Arroyo-Morales M, Seco-Calvo J. A COVID-19 Rehabilitation Prospective Surveillance Model for Use by Physiotherapists. JCM 2021;10(8):1691. Journal Website

358. NICE, RCGP and SIGN. Covid-19 rapid guideline: managing the long term effects of Covid-19. 2021 (https://www.nice.org.uk/guidance/ng188, accessed August 2022). Website

359. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021;397(10270):220-232 Journal Website

360. Heightman M, Prashar J, Hillman TE, Marks M, Livingston R, Ridsdale HA, et al. Post-COVID-19 assessment in a specialist clinical service: a 12-month, single-centre, prospective study in 1325 individuals. BMJ Open Resp Res 2021;8(1):e001041 Journal Website

361. World Physiotherapy. World Physiotherapy Response to COVID-19 Briefing Paper 9. Safe rehabilitation approaches for people living with Long COVID: physical activity and exercise. 2021. Website

362. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. BMJ 2020;m3026 Journal Website

363. Yan Z, Yang M, Lai C-L. Long COVID-19 Syndrome: A Comprehensive Review of Its Effect on Various Organ Systems and Recommendation on Rehabilitation Plans. Biomedicines 2021;9(8):966 Journal Website

364. Elder H, Prasad A, Burns GP. P177 Experiences from post COVID-19 clinic in a tertiary centre. 2021;76:A186. Journal Website

365. del Rio C, Collins LF, Malani P. Long-term Health Consequences of COVID-19. JAMA 2020;324(17):1723 Journal Website

366. Dennis A, Wamil M, Alberts J, Oben J, Cuthbertson DJ, Wootton D, et al. Multiorgan Impairment in low-risk individuals with post-COVID-19 syndrome: A prospective, community-based study. BMJ Open 2021;11(e048391) Journal

367. Raman B, Bluemke DA, Lüscher TF, Neubauer S. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. Eur Heart J 2022;43(11):1157-1172 Journal Website

368. Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med 2021;28(2):410-422 Journal Website

369. Petersen EL, Goßling A, Adam G, Aepfelbacher M, Behrendt C-A, Cavus E, et al. Multi-organ assessment in mainly non-hospitalized individuals after SARS-CoV-2 infection: The Hamburg City Health Study COVID programme. Eur Heart J 2022;43(11):1124-1137 Journal Website

370. Abbasi J. The COVID Heart—One Year After SARS-CoV-2 Infection, Patients Have an Array of Increased Cardiovascular Risks. JAMA 2022;327(12):1113 Journal Website

371. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nat Med 2022;28(3):583-590 Journal Website

372. Lindsay RK, Wilson JJ, Trott M, Olanrewaju O, Tully MA, López-Sánchez GF, et al. What are the recommendations for returning athletes who have experienced long term COVID-19 symptoms?. Ann Med 2021;53(1):1935-1944 Journal Website

373. Carda S, Invernizzi M, Bavikatte G, Bensmaïl D, Bianchi F, Deltombe T. COVID-19 pandemic. The role of physical and rehabilitation medicine specialists, a clinician's perspective. Ann Phys Rehabil Med 2020;56(4):515-524 Journal

374. Carda S, Invernizzi M, Bavikatte G, Bensmaïl D, Bianchi F, Deltombe T, et al. COVID-19 pandemic. What should Physical and Rehabilitation Medicine specialists do? A clinician's perspective. Eur J Phys Rehabil Med 2020;56(4) Journal Website

375. Sivan M, Wright S, Hughes S, Calvert M. Using condition specific patient reported outcome measures for long covid. BMJ Open 2022;o257

376. O'Connor RJ, Preston N, Parkin A, Makower S, Ross D, Gee J, et al. The COVID19 Yorkshire Rehabilitation Scale (C19YRS): Application and psychometric analysis in a postCOVID19 syndrome cohort. J Med Virol 2021;94(3):1027--1034

377. Norrefalk J-R, Borg K, Bileviciute-Ljungar I. Self-scored impairments in functioning and disability in post-COVID syndrome following mild COVID-19 infection. J Rehabil Med 2021.

378. Machado FVC, Meys R, Delbressine JM, Vaes AW, Goërtz YMJ, van Herck M, et al. Construct validity of the Post-COVID-19 Functional Status Scale in adult subjects with COVID-19. Health Qual Life Outcomes 2021;19(1)

379. Moreno-Torres L, Ventura-Alfaro C. Validation of the Post-COVID-19 functional status scale into Mexican-Spanish. J Rehabil Med Clin Commun 2021;4(1):jrmcc00069

380. Verduzco-Gutierrez M, Estores IM, Graf MJP, Barshikar S, Cabrera JA, Chang LE, et al. Models of Care for Postacute COVID-19 Clinics. Am J Phys Med Rehabil 2021;100(12):1133-1139

381. Nurek M, Rayner C, Freyer A, Taylor S, Järte L, MacDermott N, et al. Recommendations for the Recognition, Diagnosis, and Management of Patients with Post COVID-19 Condition ('Long COVID'): A Delphi Study. SSRN Electronic Journal 2021. Journal

382. Rehabilitation & Allied Health Practice Considerations Post - COVID-19. Journal Website

383. Sivan M, Parkin A, Makower S, Greenwood DC. PostCOVID syndrome symptoms, functional disability, and clinical severity phenotypes in hospitalized and nonhospitalized individuals: A crosssectional evaluation from a community COVID rehabilitation service. J Med Virol 2021;94(4):1419--1427

384. Castanares D, Kohn L, Dauvrin M, Detollenaere J, Maertens de Noordhout C, Jongh P-DEA. Long COVID: Pathophysiology–epidemiology and patient needs. 2021.

385. Sivan M, Halpin S, Hollingworth L, Snook N, Hickman K, Clifton I. Development of an integrated rehabilitation pathway for individuals recovering from COVID-19 in the community. J Rehabil Med 2020;52(8):jrm00089

386. Boutou A, Asimakos A, Kortianou E, Vogiatzis I, Tzouvelekis A. Long COVID-19 Pulmonary Sequelae and Management Considerations. J Pers Med 2021;11(9):838

387. Wassink D, van de Ven-Stevens L. Handreiking ergotherapie bij COVID-19 cliënten in de revalidatiefase. Utrecht: Ergotherapie Nederland; 2021 (https://info.ergotherapie.nl/file/download/default/6A5E0AC0401E6972DA637BB919F13500/26-01-21%20-%20Handreiking%20ergotherapie%20bij%20COVID-19%20in%20de%20herstelfase%20-%20versie%20januari%202021.pdf, accessed August 2022). Website

388. Tabacof L, Tosto-Mancuso J, Wood J, Cortes M, Kontorovich A, McCarthy D, et al. Post-acute COVID-19 Syndrome Negatively Impacts Physical Function, Cognitive Function, Health-Related Quality of Life, and Participation. Am J Phys Med Rehabil 2022;101(1):48-52

389. Ceban F, Ling S, Lui LM, Lee Y, Gill H, Teopiz KM, et al. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. Brain Behav Immun 2022;101:93-135

390. Hossain MA, Hossain KMA, Saunders K, Uddin Z, Walton LM, Raigangar V, et al. Prevalence of Long COVID symptoms in Bangladesh: A Prospective Inception Cohort Study of COVID-19 survivors. BMJ Glob Health 2021.

391. Rogers-Brown JS, Wanga V, Okoro C, Brozowsky D, Evans A, Hopwood D, et al. Outcomes Among Patients Referred to Outpatient Rehabilitation Clinics After COVID-19 diagnosis - United States, January 2020-March 2021. MMWR Morb Mortal Wkly Rep 2021;70(27)

392. Kingstone T, Taylor AK, O'Donnell CA, Atherton H, Blane DN, Chew-Graham CA. Finding the 'right' GP: a qualitative study of the experiences of people with long-COVID. BJGP Open 2020;4(5)

393. Support for rehabilitation: self-management after COVID-19-related illness, 2nd ed. Geneva: World Health Organization; 2021 (https://www.who.int/publications/m/item/support-for-rehabilitation-self-management-after-covid-19-related-illness, accessed August 2022). Website

394. O'Brien H, Tracey MJ, Ottewill C, O\textquoterightBrien ME, Morgan RK, Costello RW, et al. An integrated multidisciplinary model of COVID-19 recovery care. Irish Journal of Medical Science (1971 -) 2020;190(2):461-468

395. Whelehan DF, Algeo N, Brown DA. Leadership through crisis: fighting the fatigue pandemic in healthcare during COVID-19. BMJ Leader 2021;5(2):108-112

396. Ladds E, Rushforth A, Wieringa S, Taylor S, Rayner C, Husain L, et al. Developing services for long Covid: lessons from a study of wounded healers. Clin Med 2020.

397. Duncan LJ, Cheng KF. Modifications to the delivery of NHS face-to-face general practice consultations during the COVID-19 pandemic in England. F1000Research 2021;10:261

398. Ahmed I, Inam AB, Belli S, Ahmad J, Khalil W, Jafar MM. Effectiveness of aerobic exercise training program on cardio-respiratory fitness and quality of life in patients recovered from COVID-19. Eur J Physiother 2021;1-6

399. Centres for Disease Control and Prevention. Post-COVID Conditions: Information for Healthcare Providers. 2021.

400. Bateman L, Bested AC, Bonilla HF. Myalgic encephalomyelitis/chronic fatigue syndrome: essentials of diagnosis and management. Elsevier 2021;96(11):2861-2878

401. Davenport TE, Stevens SR, Baroni K, Van Ness M, Snell CR. Diagnostic accuracy of symptoms characterising chronic fatigue syndrome. Disabil Rehabil 2011;33(19-20):1768-1775

402. Cotler J, Holtzman C, Dudun C, Jason L. A Brief Questionnaire to Assess Post-Exertional Malaise. Diagnostics 2018;8(3):66

403. Davenport TE, Stevens SR, Stevens J, Snell CR, VanNess JM. Lessons from Myalgic Encephalomyelitis/Chronic Fatigue Syndrome for Long COVID: Postexertional Symptom Exacerbation is an Abnormal Response to Exercise/Activity. J Orthop Sports Phys Ther 2022.

404. Jason LA, Holtzman CS, Sunnquist M, Cotler J. The development of an instrument to assess post-exertional malaise in patients with myalgic encephalomyelitis and chronic fatigue syndrome. J Health Psychol 2018;26(2):238-248

405. O'Connor RJ, Preston N, Parkin A, Makower S, Ross D, Gee J, et al. The COVID19 Yorkshire Rehabilitation Scale (C19YRS): Application and psychometric analysis in a postCOVID19 syndrome cohort. J Med Virol 2021;94(3):1027-1034

406. Francis A, Harris J, Coleman J. Rehabilitation for clients with Post COVID-19 Condition (Long COVID): Guidance for Canadian Rehabilitation and Exercise Professionals. Version 1. August 2021. Website

407. Humphreys H, Kilby L, Kudiersky N, Copeland R. Long Covid and the role of physical activity: a qualitative study. BMJ Open 2020.

408. Ziauddeen N, Gurdasani D, O'Hara ME, Hastie C, Roderick P, Yao G, et al. Characteristics and impact of Long Covid: Findings from an online survey. PLoS One 2022;17(3):e0264331

409. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re\textquoterightem Y, et al. Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact. EClinicalMedicine 2021;38:101019. Website

410. Kos D, van Eupen I, Meirte J, Van Cauwenbergh D, Moorkens G, Meeus M, et al. Activity Pacing Self-Management in Chronic Fatigue Syndrome: A Randomized Controlled Trial. The American Journal of Occupational Therapy 2015;69(5):6905290020p1--6905290020p11

411. Royal College of Occupational Therapists. How to conserve your energy. (https://www.rcot.co.uk/conserving-energy, accessed August 2022). Website

412. Royal College of Occupational Therapists. A quick guide for occupational therapists: Occupational therapy and adults with Long Covid (Post COVID-19 Syndrome/Condition). 2021 (https://www.rcot.co.uk/post-covid-syndrome-long-covid#rcot-resources, accessed August 2022). Website

413. Davenport TE, Stevens SR, Van Ness JM. Lessons from Myalgic Encephalomyelitis/Chronic Fatigue Syndrome for Long COVID Part 4: Heart Rate Monitoring to Manage Postexertional Symptom Exacerbation. JOSPT 2022. Website

414. Davenport TE, Stevens SR, Van Ness JM. Lessons from Myalgic Encephalomyelitis/Chronic Fatigue Syndrome for Long COVID Part 3: ``Energy System First Aid'' for People with Postexertional Symptom Exacerbation. JPOST 2022. Website

415. Décary S, Gaboury I, Poirier S. Humility and Acceptance: Working Within Our Limits with Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. J Orthop Sports Phys 2021;51(5):197-200

416. Li S, Wang R, Zhang Y, Zhang X, Layon AJ, Li Y, et al. Symptom combinations associated with outcome and therapeutic effects in a cohort of cases with SARS. Am J Chin Med 2006;34(06):937-947 Journal Website

417. Friedman N, Alter H, Hindiyeh M, Mendelson E, Shemer Avni Y, Mandelboim M. Human coronavirus infections in Israel: Epidemiology, clinical symptoms and summer seasonality of hcov-hku1. Viruses 2018;10(10):515 Journal Website

418. Najafi S, Rajaei E, Moallemian R, Nokhostin F. The potential similarities of COVID-19 and autoimmune disease pathogenesis and therapeutic options: new insights approach. Clin Rheumatol 2020;39(11):3223-3235 Journal Website

419. Parisi S, Borrelli R, Bianchi S, Fusaro E. Viral arthritis and COVID-19. Lancet Rheumatol 2020;2(11):e655-e657 Journal Website

420. Vlachoyiannopoulos PG, Magira E, Alexopoulos H, Jahaj E, Theophilopoulou K, Kotanidou A, et al. Autoantibodies related to systemic autoimmune rheumatic diseases in severely ill patients with COVID-19. Ann Rheum Dis 2020;79(12):1661-1663 Journal Website

421. Ouedraogo F, Navara R, Thapa R, Patel KG. Reactive Arthritis Post-SARS-CoV-2. Cureus 2021;13(9):e18139. Journal Website

422. Zhang Z, Huang C, Jiang Q. Guidelines for the diagnosis and treatment of osteoarthritis in China (2019 edition). Ann Transl Med 2020;8(19)

423. Pugliese M, Wolff A. The Value of Communication, Education, and Self-Management in Providing Guideline-Based Care: Lessons Learned from Musculoskeletal Telerehabilitation During the COVID-19 Crisis. HSS J 2021;16(S1):160-163 Journal Website

424. Gotzsche PC, Johansen HK. Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis. Cochrane Database Syst Rev 1998;(2):CD000189. Journal Website

425. van Walsem A, Pandhi S, Nixon RM, Guyot P, Karabis A, Moore RA. Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis. Arthritis Res Ther 2015;17(1) Journal

426. Lau HM-C, Ng GY-F, Jones AY-M, Lee EW-C, Siu EH-K, Hui DS-C. A randomised controlled trial of the effectiveness of an exercise training program in patients recovering from severe acute respiratory syndrome. Aust J Physiother 2005;51(4):213-219 Journal Website

427. Bartels EM, Juhl CB, Christensen R, Hagen KB, Danneskiold-Samsøe B, Dagfinrud H, et al. Aquatic exercise for the treatment of

knee and hip osteoarthritis. Cochrane Database Syst Rev 2016;(3):CD005523. Journal Website

428. Hurley M, Dickson K, Hallett R, Grant R, Hauari H, Walsh N, et al. Exercise interventions and patient beliefs for people with hip, knee or hip and knee osteoarthritis: a mixed methods review. Cochrane Database Syst Rev 2018;(4):CD010842. Journal Website

429. Regnaux JP, Davergne T, Palazzo C, Rolen A, Rannou F, Boutron I, et al. Exercise Programme for ankylosing spondylitis. Cochrane Database Sys Rev 2019;10(10):CD011321.

430. Lund H, Weile U, Christensen R, Rostock B, Downey A, Bartels EM, et al. A randomized controlled trial of aquatic and land-based exercise in patients with knee osteoarthritis. Acta Derm Venereol 2008;40(2):137-144 Journal

431. Rogind H, Bibow-Nielsen B, Jensen B, Moller HC, Frimodt-Moller H, Bliddal H. The effects of a physical training program on patients with osteoarthritis of the knee. Arch Phys Med Rehabil 1998;79(11):1421-1427 Journal

432. CKS is only available in the UK. Website

433. Ozalevli S., Ozden A., Itil O., Akkoclu A.. Comparison of the Sit-to-Stand Test with 6min walk test in patients with chronic obstructive pulmonary disease. Respir Med 2006;101(2):286-293 Journal Website

434. Zanini A, Crisafulli E, D'Andria M, Gregorini C, Cherubino F, Zampogna E, et al. Minimum Clinically Important Difference in 30-s Sit-to-Stand Test After Pulmonary Rehabilitation in Subjects With COPD. Respir Care 2019;64(10):1261-1269 Journal Website

435. Betschart M, Rezek S, Unger I, Beyer S, Gisi D, Shannon H, et al. Feasibility of an Outpatient Training Program after COVID-19. IJERPH 2021;18(8):3978 Journal Website

436. Wilson RC, Jones PW. A comparison of the visual analogue scale and modified Borg scale for the measurement of dyspnoea during exercise. Clin Sci 1989;76(3):277-282 Journal Website

437. Banzett RB, O'Donnell CR, Guilfoyle TE, Parshall MB, Schwartzstein RM, Meek PM, et al. Multidimensional Dyspnea Profile: an instrument for clinical and laboratory research. Eur Respir J 2015;45(6):1681-1691 Journal Website

438. Stenton C.. The MRC breathlessness scale. Occup Med 2008;58(3):226-227 Journal Website

439. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14(5):377-381 Journal Website

440. Spathis A, Booth S, Moffat C, Hurst R, Ryan R, Chin C, et al. The Breathing, Thinking, Functioning clinical model: a proposal to facilitate evidence-based breathlessness management in chronic respiratory disease. NPJ Prim Care Resp Med 2017;27(1) Journal Website

441. Wang TJ, Chau B, Lui M, Lam G-T, Lin N, Humbert S. Physical Medicine and Rehabilitation and Pulmonary Rehabilitation for COVID-19. Am J Phys Med Rehabil 2020;99(9):769-774 Journal Website

442. Daynes E, Gerlis C, Chaplin E, Gardiner N, Singh SJ. Early experiences of rehabilitation for individuals post-COVID to improve fatigue, breathlessness exercise capacity and cognition – A cohort study. Chron Respir Dis 2021;18 Pubmed Website

443. Li J, Xia W, Zhan C, Liu S, Yin Z, Wang J, et al. A telerehabilitation programme in post-discharge COVID-19 patients (TERECO): a randomised controlled trial. Thorax 2022;77(7):697-706 Journal Website

444. Nopp S, Moik F, Klok FA, Gattinger D, Petrovic M, Vonbank K, et al. Outpatient Pulmonary Rehabilitation in Patients with Long COVID Improves Exercise Capacity, Functional Status, Dyspnea, Fatigue, and Quality of Life. Respiration 101(6):593-601 Journal Website

445. Barbara C, Clavario P, De Marzo V, Lotti R, Guglielmi G, Porcile A, et al. Effects of exercise rehabilitation in patients with long coronavirus disease 2019. Eur J Prev Cardiol 2022;29(7):e258-e260 Pubmed Journal

446. Bruton A, Lee A, Yerdley L, Raferty J, Arden-Close E, Kirbby S. Physiotherapy breathing retraining for asthma: a randomised controlled trial. Lancet Respir Med 6(1):19-28

447. Méndez R, Balanzá-Martínez V, Luperdi SC, Estrada I, Latorre A, González-Jiménez P, et al. Short-term neuropsychiatric outcomes and quality of life in COVID-19 survivors. J Intern Med 2021;290(3):621-631

448. Miskowiak K, Johnsen S, Sattler S, Nielsen S, Kunalan K, Rungby JEA. Cognitive impairments four months after COVID-19 hospital discharge: Pattern, severity and association with illness variables. Eur Neuropsychopharmacol 2021;46:39-48

449. Crivelli L, Palmer K, Calandri I, Guekht A, Beghi E, Carroll WEA. Changes in cognitive functioning after COVID-19: A systematic review and meta-analysis. Alzheimers Dement

450. Langton-Frost N, Brodsky MB. Speech-language pathology approaches to neurorehabilitation in acute care during COVID-19: Capitalizing on neuroplasticity. PM&R 2022;14(2):217-226

451. Raman B, Cassar MP, Tunnicliffe EM, Filippini N, Griffanti L, Alfaro-Almagro FEA. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. EClinicalMedicine 2021;31:100683

452. Almeria M, Cejudo JC, Sotoca J, Deus J, Krupinski J. Cognitive profile following COVID-19 infection: Clinical predictors leading to neuropsychological impairment. Brain Behav Immun 2020;9:100163

453. Liu Y-H, Chen Y, Wang Q-H, Wang L-R, Jiang L, Yang YEA. One-year trajectory of cognitive changes in older survivors of COVID-19 in Wuhan, China: a longitudinal cohort study. JAMA Neurol 2022;79(5):509-517

454. Amini A, Vaezmousavi M, Shirvani H. The effectiveness of cognitive-motor training on reconstructing cognitive health components in older male adults, recovered from the COVID-19. Neurol Sci 2022;43(2):1395-1403

455. Cysique LA, Łojek E, Cheung TC-K, Cullen B, Egbert AR, Evans JEA. Assessment of neurocognitive functions, olfaction, taste, mental, and psychosocial health in COVID-19 in adults: Recommendations for harmonization of research and implications for clinical practice. J Int Neuropsychol Soc 2022;28(6):642-660

456. Fernández-Castañeda A, Lu P, Geraghty AC, Song E, Lee M-H, Wood JEA. Mild respiratory SARS-CoV-2 infection can cause multi-lineage cellular dysregulation and myelin loss in the brain. BioRxiv 2022.

457. Evans RA, McAuley H, Harrison EM, Shikotra A, Singapuri A, Sereno MEA. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. Lancet Respir Med 2021;9(11):1275-1287

458. Graham E, Clark J, Orban Z, Lim P, Szymanski A, Taylor C. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 “long haulers”. Ann Clin Transl Neurol 2021;8(5):1073-1085

459. Krishnan K, Miller AK, Reiter K, Bonner-Jackson A. Neurocognitive profiles in patients with persisting cognitive symptoms associated with COVID-19. Arch Clin Neuropsychol 2022;37(4):729-737

460. Whiteside DM, Basso MR, Naini SM, Porter J, Holker E, Waldron EEA. Outcomes in post-acute sequelae of COVID-19 (PASC) at 6 months post-infection Part 1: Cognitive functioning. Clin Neuropsychol 2022;36(4):806-828

461. Sandmann FG, Tessier E, Lacy J, Kall M, Van Leeuwen E, Charlett A, et al. Long-term health-related quality of life in non-hospitalised COVID-19 cases with confirmed SARS-CoV-2 infection in England: Longitudinal analysis and cross-sectional comparison with controls. Clin Infect Dis 2022. Pubmed Journal

462. Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: The Fatigue Assessment Scale. J Psychosom Res 2003;54(4):345-352

463. Butt Z, Lai J-S, Rao D, Heinemann AW, Bill A, Cella D. Measurement of fatigue in cancer, stroke, and HIV using the functional assessment of chronic illness therapy—fatigue (FACIT-F) scale. J Psychosom Res 2013;74(1):64-68

464. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46(10):1121-1123

465. NIHR. Living with Covid19 – Second review. 2021;2022 Journal Website

466. Larun L, Brurberg KG, Odgaard-Jensen J, Price JR. Exercise therapy for chronic fatigue syndrome. Cochrane Database Sys Rev (10)

467. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. Cochrane Database Sys Rev 2012.(11)

468. Hulme K, Safari R, Thomas S, Mercer T, White C, Van der Linden M, et al. Fatigue interventions in long term, physical health conditions: a scoping review of systematic reviews. PloS one 2018;13(10):e0203367

469. Reid H, Ridout AJ, Tomaz SA, Kelly P, Jones N. Benefits outweigh the risks: a consensus statement on the risks of physical activity for people living with long-term conditions. Br J Sports Med 2022;56(8):427-438

470. Hayden MC, Limbach M, Schuler M, Merkl S, Schwarzl G, Jakab K, et al. Effectiveness of a three-week inpatient pulmonary rehabilitation program for patients after COVID-19: A prospective observational study. Int J Environ Res Public Health 2021;18(17):9001

471. Maniscalco M, Fuschillo S, Ambrosino P, Martucci M, Papa A, Matera MG, et al. Preexisting cardiorespiratory comorbidity does not preclude the success of multidisciplinary rehabilitation in post-COVID-19 patients. Resp Med 2021;184:106470

472. Kuut TA, Müller F, Aldenkamp A, Assmann-Schuilwerve E, Braamse A, Geerlings SE, et al. A randomised controlled trial testing the efficacy of Fit after COVID, a cognitive behavioural therapy targeting severe post-infectious fatigue following COVID-19 (ReCOVer): study protocol. Trials 2021;22(1):1-15

473. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine 2021;38:101019

474. Maddocks M, Brown D. Critically appraised paper: In people reporting dyspnoea following COVID-19 hospitalisation, additional telerehabilitation is more effective at improving exercise capacity, muscle strength and the physical component of quality of life than education alone [commentary]. J Physiother 2021;68(1):70 Journal

475. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme (mhGAP). Geneva: World Health Organization 2016.

476. Mazza MG, Zanardi R, Palladini M, Rovere-Querini P, Benedetti F. Rapid response to selective serotonin reuptake inhibitors in post-COVID depression. Eur Neuropsychopharmacol 2022;54:1-6

477. mhGAP Evidence Resource Centre. Geneva: World Health Organization 2015. Website

478. Carpenter JK, Andrews LA, Witcraft SM, Powers MB, Smits JA, Hofmann SG. Cognitive behavioral therapy for anxiety and related disorders: A meta-analysis of randomized placebo-controlled trials. Depress Anxiety 2018;35(6):502-514

479. Usmani ZA, Carson KV, Heslop K, Esterman AJ, De Soyza A, Smith BJ. Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease. Cochrane Database Sys Rev (3)

480. Shabahang R, Bagheri Sheykhangafshe F, Dadras M, Seyed Noori SZ. Effectiveness of Video-Based Cognitive-Behavioral Intervention on Health Anxiety and Anxiety Sensitivity of Individuals with High Levels of COVID-19 Anxiety. J Clin Psychol 2021;13(2):33-44

481. Li J, Li X, Jiang J, Xu X, Wu J, Xu Y. & Xu, X.(2020). The effect of cognitive behavioral therapy on depression, anxiety, and stress in patients with COVID-19: a randomized controlled trial. Front Psychiatry 1096

482. Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study. Complement Ther Med 2020;39:101166

483. Stavrou VT, Tourlakopoulos KN, Vavougios GD, Papayianni E, Kiribesi K, Maggoutas S, et al. Eight weeks unsupervised pulmonary rehabilitation in previously hospitalized of SARS-CoV-2 infection. J Pers Med 2021;11(8):806

484. Pollok J, Van Agteren JE, Esterman AJ, Carson-Chahhoud KV. Psychological therapies for the treatment of depression in chronic obstructive pulmonary disease. Cochrane Database Sys Rev 2019.(3)

485. Schell LK, Monsef I, Wöckel A, Skoetz N. Mindfulness-based stress reduction for women diagnosed with breast cancer. Cochrane Database Sys Rev 2019.(3)

486. Macpherson K, Cooper K, Harbour J, Mahal D, Miller C, Nairn M. Experiences of living with long COVID and of accessing healthcare services: a qualitative systematic review. BMJ open 2022;12(1):e050979

487. Spielmanns M, Pekacka-Egli A-M, Schoendorf S, Windisch W, Hermann M. Effects of a comprehensive pulmonary rehabilitation in severe post-COVID-19 patients. Int J Environ Res Public Health 2021;18(5):2695

488. Sorokowska A, Drechsler E, Karwowski M, Hummel T. Effects of olfactory training: a meta-analysis. Rhinology 2017;55(1):17-26

489. Goodman BP, Khoury JA, Blair JE, Grill MF. COVID-19 dysautonomia. Front Neurol 2021;12:624968

490. Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton REA. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. Clin Med 2021;21(1):e63

491. Shouman K, Vanichkachorn G, Cheshire WP, Suarez MD, Shelly S, Lamotte GEA. Autonomic dysfunction following COVID-19 infection: an early experience. Clinical Autonomic Research 2021;31(3):385-394

492. Freeman R, Abuzinadah AR, Gibbons C, Jones P, Miglis MG, Sinn DI. Orthostatic hypotension: JACC state-of-the-art review. J Am Coll Cardiol 2018;72(11):1294-1309

493. Dawson C, Capewell R, Ellis S, Matthews S, Adamson S, Wood MEA. Dysphagia presentation and management following coronavirus disease 2019: an acute care tertiary centre experience. J Laryngol Otol 2020;134(11):981-986

494. Archer SK, Iezzi CM, Gilpin L. Swallowing and voice outcomes in patients hospitalized with COVID-19: an observational cohort study. Arch Phys Med Rehabil 2021;102(6):1084-1090

495. Brodsky MB, Huang M, Shanholtz C, Mendez-Tellez PA, Palmer JB, Colantuoni EEA. Recovery from dysphagia symptoms after oral endotracheal intubation in acute respiratory distress syndrome survivors. A 5-year longitudinal study. Ann Am Thorac Soc 2017;14(3):376-383

496. Verma H, Shah J, Akhilesh K, Shukla B. Patients' perspective about speech, swallowing and hearing status post-SARS-CoV-2 (COVID-19) recovery: E-survey. Eur Arch Otorhinolaryngol 2022;279(5):2523-2532

497. Grilli GM, Giancaspro R, Del Colle A, Quarato CMI, Lacedonia D, Foschino Barbaro MEA. Dysphagia in non-intubated patients affected by COVID-19 infection. Eur Arch Otorhinolaryngol 2022;279(1):507-513

498. Marchese MR, Ausili Cefaro C, Mari G, Proietti I, Carfì A, Tosato MEA. Oropharyngeal dysphagia after hospitalization for COVID-19 disease: our screening results. Dysphagia 2022;37(2):447-453

499. Wheeler-Hegland K, Ashford J, Frymark T, McCabe D, Mullen R, Musson NEA. Evidence-based systematic review: Oropharyngeal dysphagia behavioral treatments. Part II--impact of dysphagia treatment on normal swallow function. J Rehabil Res Dev 2009;46(2)

500. Speyer R, Baijens L, Heijnen M, Zwijnenberg I. Effects of therapy in oropharyngeal dysphagia by speech and language therapists: a systematic review. Dysphagia 25(1):40-65

501. Patel DA, Sharda R, Hovis KL, Nichols EE, Sathe N, Penson DEA. Patient-reported outcome measures in dysphagia: a systematic review of instrument development and validation. Dis Esophagus 2017;30(5):1-23

502. Beck AM, Kjaersgaard A, Hansen T, Poulsen I. Systematic review and evidence based recommendations on texture modified foods and thickened liquids for adults (above 17 years) with oropharyngeal dysphagia–An updated clinical guideline. Clin Nutr 37(6):1980-1991

503. Ayuse T, Ayuse T, Ishitobi S, Kurata S, Sakamoto E, Okayasu IEA. Effect of reclining and chin-tuck position on the coordination between respiration and swallowing. J Oral Rehabil 2006;33(6):402-408

504. Perry JL, Bae Y, Kuehn DP. Effect of posture on deglutitive biomechanics in healthy individuals. Dysphagia 2012;27(1):70-80

505. Logemann JA, Kahrilas P, Kobara M, Vakil N. The benefit of head rotation on pharyngoesophageal dysphagia. Arch Phys Med Rehabil 1989;70(10):767-771

506. Bülow M, Olsson R, Ekberg O. Supraglottic swallow, effortful swallow, and chin tuck did not alter hypopharyngeal intrabolus pressure in patients with pharyngeal dysfunction. Dysphagia 2002;17(3):197-201

507. Oh J-C. Effect of the head extension swallowing exercise on suprahyoid muscle activity in elderly individuals. Exp Gerontol 2018;110:133-138

508. McCulloch TM, Hoffman MR, Ciucci MR. High-resolution manometry of pharyngeal swallow pressure events associated with head turn and chin tuck. Ann Otol Rhinol Laryngol 2010;119(6):369-376

509. Ekberg O. Posture of the head and pharyngeal swallowing. Acta Radiologica. Diagnosis 1986;27(6):691-696

510. Solazzo A, Monaco L, Del Vecchio L, Tamburrini S, Iacobellis F, Berritto DEA. Investigation of compensatory postures with videofluoromanometry in dysphagia patients. World J Gastroenterol 2012;18(23):2973

511. Lazarus CL. History of the use and impact of compensatory strategies in management of swallowing disorders. Dysphagia 2017;32(1):3-10

512. Martin BJ, Logemann JA, Shaker R, Dodds WJ. Normal laryngeal valving patterns during three breath-hold maneuvers: a pilot investigation. Dysphagia 1993;8(1):11-20

513. Benfield JK, Everton LF, Bath PM, England TJ. Does therapy with biofeedback improve swallowing in adults with dysphagia? A systematic review and meta-analysis. Arch Phys Med Rehabil 2019;100(3):551-561

514. McKenna VS, Zhang B, Haines MB, Kelchner LN. A systematic review of isometric lingual strength-training programs in adults with and without dysphagia. Am J Speech Lang Pathol 26(2):524-539

515. Park JS, Hwang NK. Chin tuck against resistance exercise for dysphagia rehabilitation: a systematic review. J Oral Rehabil 2021;48(8):968-977

516. Bath PM, Lee HS, Everton LF. Swallowing therapy for dysphagia in acute and subacute stroke. Cochrane Database Syst Rev 2018.(10)

517. Asiaee M, Vahedian-Azimi A, Atashi SS, Keramatfar A, Nourbakhsh M. Voice quality evaluation in patients with COVID-19: An acoustic analysis. J Voice 2020.

518. Cantarella G, Aldè M, Consonni D, Zuccotti G, Di Berardino F, Barozzi S, et al. Prevalence of Dysphonia in Non hospitalized Patients with COVID-19 in Lombardy, the Italian Epicenter of the Pandemic. J Voice 2021.

519. Jafari N, Salehi A, Izadi F, Moghadam ST, Ebadi A, Dabirmoghadam P, et al. Vocal function exercises for muscle tension dysphonia: auditory-perceptual evaluation and self-assessment rating. J Voice 2017;31(4):e25-e31

520. Deary IJ, Wilson JA, Carding PN, MacKenzie K. VoiSS: a patient-derived voice symptom scale. J Psychosom Res 2003;54(5):483-489

521. Jacobson BH, Johnson A, Grywalski C, Silbergleit A, Jacobson G, Benninger MS, et al. The voice handicap index (VHI) development and validation. Am J Speech Lang Path 1997;6(3):66-70

522. Hogikyan ND, Sethuraman G. Validation of an instrument to measure voice-related quality of life (V-RQOL). J Voice 1999;13(4):557-569

523. Alves M, Krueger E, Pillay B, Van Lierde K, Van der Linde J. The effect of hydration on voice quality in adults: a systematic review. J Voice 33(1):e13-e28

524. Christensen KA, Christensen J, Eskildsen SJ. Exploring the Ability to Perform Activities of Daily Living and Cognitive Status after Hospitalization with COVID-19: A Multiple Case Study. Occup Ther Int 2022.

525. Wong J, Kudla A, Pham T, Ezeife N, Crown D, Capraro PEA. Employment Consequences of COVID-19 on “Long-Haul” Survivors. Arch Phys Med Rehabil 2021;102(10):e66

526. 2019 Healthcare Professionals' Consensus Statement for Action Statement for Health and Work. Website

527. Waddell G, Burton AK. Is work good for your health and well-being?. The Stationary Office 2006.

528. Pizarro-Pennarolli C, Sánchez-Rojas C, Torres-Castro R, Vera-Uribe R, Sanchez-Ramirez DC, Vasconcello-Castillo LEA. Assessment of activities of daily living in patients post COVID-19: a systematic review. PeerJ 2021;9:e11026

529. Rayner C, Campbell R. Long Covid Implications for the workplace. Occup Med 2021.

530. Barker-Davies RM, O'Sullivan O, Senaratne KPP, Baker P, Cranley M, Dharm-Datta SEA. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. Br J Sports Med 2020;54(16):949-959

531. Hobson J, Smedley J. Fitness for Work: The Medical Aspects. Oxford University Press, USA 2019.

532. Prieur G, Combret Y, Medrinal C, Arnol N, Bonnevie T, Gravier F-EEA. Energy conservation technique improves dyspnoea when patients with severe COPD climb stairs: a randomised crossover study. Thorax 2020;75(6):510-512

533. Therapists R. How to conserve your energy: Practical advice for people during and after having COVID-19. Br J Occup Ther 2020.

534. Kendall NA, Burton AK, Main CJ, Watson P. Tackling musculoskeletal problems: a guide for clinic and workplace-identifying obstacles using the psychosocial flags framework. The Stationary Office 2009.

535. Kendall N, Burton K, Lunt J, Mellor N, Daniels K. Developing an intervention toolbox for common health problems in the workplace. 2015.

536. Waddell G, Burton AK, Kendall NA. Vocational rehabilitation–what works, for whom, and when?(Report for the Vocational Rehabilitation Task Group). The Stationary Office 2008.

537. World Health Organization. Q&A: Ethics and COVID-19: resource allocation and priority setting. 2020. Website

538. Pfefferbaum B., North CS. Mental Health and the Covid-19 Pandemic. N Engl J Med 2020. Pubmed Journal Website

539. World Health Organization. International guidelines for certification and classification (coding) of COVID-19 as cause of death. Based on ICD. International Statistical Classification of Diseases. 2020. Website

540. International Severe Acute Respiratory and Emerging Infection Consortium. Clinical Characterisation Protocol. 2020 (https://isaric.org/research/covid-19-clinical-research-resources/clinical-characterisation-protocol-ccp/, accessed August 2022). Website

541. Diagnostic testing for SARS-CoV-2. Geneva: World Health Organization; 2020 (WHO-2019-nCoV-laboratory-2020.6;

https://www.who.int/publications/i/item/diagnostic-testing-for-sars-cov-2) Website

542. Gordon A, Rabold E, Thirumala R, Husain AA, Patel S, Cheema T. Prone Positioning in ARDS. Critical care nursing quarterly 2019;42(4):371-375 Pubmed Journal

543. Munshi L, Del Sorbo L, Adhikari NKJ, Hodgson CL, Wunsch H, Meade MO, et al. Prone Position for Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. Annals of the American Thoracic Society 2017;14(Supplement_4):S280-S288 Pubmed Journal

544. Current COVID-19 situation: overview of SARS-CoV-2 circulating variants. Geneva: World Health Organization; 2023 Website

545. Weatherald J, Parhar KKS, Al Duhailib Z, Chu DK, Granholm A, Solverson K, et al. Efficacy of awake prone positioning in patients with covid-19 related hypoxemic respiratory failure: systematic review and meta-analysis of randomized trials. BMJ 379:e071966 Journal Website

546. Weatherald J, Parhar K. Awake Prone Positioning for COVID-19 Hypoxemic Respiratory Failure: A Systematic Review and Meta-Analysis of Randomised Trials. 2023-03-01.

547. Weekly epidemiological update on COVID-19. 2023-07-17. Website

548. WHO Director-General's opening remarks at the media briefing – 5 May 2023. 2023-05-05. Website

549. Feikin DR, Higdon MM, Abu-Raddad LJ, Andrews N, Araos R, Goldberg Y, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. Lancet (London, England) 399(10328):924-944 Pubmed Journal

550. Bruel T, Stéfic K, Nguyen Y, Toniutti D, Staropoli I, Porrot F, et al. Longitudinal analysis of serum neutralization of SARS-CoV-2 Omicron BA.2, BA.4, and BA.5 in patients receiving monoclonal antibodies. Cell reports. Medicine 2022;3(12):100850 Pubmed Journal

551. Menegale F, Manica M, Zardini A, Guzzetta G, Marziano V, d'Andrea V, et al. Evaluation of Waning of SARS-CoV-2 Vaccine-Induced Immunity: A Systematic Review and Meta-analysis. JAMA network open 6(5):e2310650 Pubmed Journal

552. Arabi M, Al-Najjar Y, Mhaimeed N, Salameh MA, Paul P, AlAnni J, et al. Severity of the Omicron SARS-CoV-2 variant compared with the previous lineages: A systematic review. Journal of cellular and molecular medicine 27(11):1443-1464 Pubmed Journal

553. Relan P, Motaze NV, Kothari K, Askie L, Le Polain O, Van Kerkhove MD, et al. Severity and outcomes of Omicron variant of SARS-CoV-2 compared to Delta variant and severity of Omicron sublineages: a systematic review and metanalysis. BMJ global health 8(7) Pubmed Journal

554. Levy N, Koppel JH, Kaplan OR, Yechiam H, Shahar-Nissan K, Cohen NK, et al. Severity and Incidence of Multisystem Inflammatory Syndrome in Children During 3 SARS-CoV-2 Pandemic Waves in Israel. JAMA 2022;327(24):2452-2454 Pubmed Journal

555. Long-term neurological sequelae of SARS-CoV-2 infection. Nature medicine 2022;28(11):2269-2270 Pubmed Journal

556. Beghi E, Giussani G, Westenberg E, Allegri R, Garcia-Azorin D, Guekht A, et al. Acute and post-acute neurological manifestations of COVID-19: present findings, critical appraisal, and future directions. Journal of neurology 2022;269(5):2265-2274 Pubmed Journal

557. Pun BT, Badenes R, Heras La Calle G, Orun OM, Chen W, Raman R, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. The Lancet. Respiratory medicine 2021;9(3):239-250 Pubmed Journal

558. Beaney T, Neves AL, Alboksmaty A, Ashrafian H, Flott K, Fowler A, et al. Trends and associated factors for Covid-19 hospitalisation and fatality risk in 2.3 million adults in England. Nature communications 2022;13(1):2356 Pubmed Journal

559. Wang C, Liu B, Zhang S, Huang N, Zhao T, Lu Q-B, et al. Differences in incidence and fatality of COVID-19 by SARS-CoV-2 Omicron variant versus Delta variant in relation to vaccine coverage: A world-wide review. Journal of medical virology 2023;95(1):e28118 Pubmed Journal

560. McDonald SA, Miura F, Vos ERA, van Boven M, de Melker HE, van der Klis FRM, et al. Estimating the asymptomatic proportion of SARS-CoV-2 infection in the general population: Analysis of nationwide serosurvey data in the Netherlands. European journal of epidemiology 2021;36(7):735-739 Pubmed Journal

561. Shang W, Kang L, Cao G, Wang Y, Gao P, Liu J, et al. Percentage of Asymptomatic Infections among SARS-CoV-2 Omicron Variant-Positive Individuals: A Systematic Review and Meta-Analysis. Vaccines 10(7) Pubmed Journal

562. World Health Organization. Tracking SARS-CoV-2 variants. 2023-07-19. Website

563. Updated working definitions and primary actions for SARS-CoV-2 variants. World Health Organization 2023-03-15. Journal Website

564. Update 84: Current COVID-19 situation: overview of SARS-CoV-2 circulating variants. World Health Organization 2023-02-23. Journal Website

565. Natarajan A, Shetty A, Delanerolle G, Zeng Y, Zhang Y, Raymont V, et al. A systematic review and meta-analysis of long COVID symptoms. Systematic reviews 2023;12(1):88 Pubmed Journal

566. O'Mahoney LL, Routen A, Gillies C, Ekezie W, Welford A, Zhang A, et al. The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. EClinicalMedicine 2023;55:101762 Pubmed Journal

567. Pellegrino R, Chiappini E, Licari A, Galli L, Marseglia GL. Prevalence and clinical presentation of long COVID in children: a systematic review. European journal of pediatrics 2022;181(12):3995-4009 Pubmed Journal

568. Hossain MM, Das J, Rahman F, Nesa F, Hossain P, Islam AMK, et al. Living with "long COVID": A systematic review and meta-synthesis of qualitative evidence. PloS one 2023;18(2):e0281884 Pubmed Journal

569. Tsampasian V, Elghazaly H, Chattopadhyay R, Debski M, Naing TKP, Garg P, et al. Risk Factors Associated With Post-COVID-19 Condition: A Systematic Review and Meta-analysis. JAMA internal medicine 2023;183(6):566-580 Pubmed Journal

570. Wulf Hanson S, Abbafati C, Aerts JG, Al-Aly Z, Ashbaugh C, Ballouz T, et al. Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021. JAMA 328(16):1604-1615 Pubmed Journal

571. Weatherald J, Parhar K. Awake Prone Positioning for COVID-19 Hypoxemic Respiratory Failure: A Systematic Review and Meta-Analysis of Randomised Trials (update for WHO).

572. Al-Aly Z, Davis H, McCorkell L. Long COVID science, research and policy. Nat Med 30, 2148–2164. 2024. Website

573. A clinical case definition of post COVID-19 condition by a Delphi consensus. World Health Organization. WHO Reference Number: WHO/2019-nCoV/Post_COVID-19_condition/Clinical_case_definition/2021.1. 2021. Website

574. A clinical case definition for post COVID-19 condition in children and adolescents by expert consensus. World Health Organization. WHO Reference Number: WHO/2019-nCoV/Post_COVID-19_condition/CA/Clinical_case_definition/2023.1. 2023. Website

575. Vos T. Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021. 2022. Website

576. Ford ND, Slaughter D, Edwards D. Long COVID and Significant Activity Limitation Among Adults, by Age — United States, June 1–13, 2022, to June 7–19, 2023. 2023. Website

577. Tsampasian V. Risk Factors Associated With Post-COVID-19 Condition: A Systematic Review and Meta-analysis. 2023. Website

578. Peluso MJ, Deeks SG. Mechanisms of long COVID and the path toward therapeutics. Cell. 2024;187(20):5500-5529. 2024. Website

579. Byambasuren O, Stehlik P, Clark J. Effect of covid-19 vaccination on long covid: systematic review. BMJ Medicine 2023;2:e000385. 2023. Website

580. Langford BJ, So M, Leung V, Raybardhan S, Lo J, Kan T, et al. Predictors and microbiology of respiratory and bloodstream bacterial infection in patients with COVID-19: living rapid review update and meta-regression. Clin Microbiol Infect 2022;28(4):491-501 Pubmed Journal

581. Summary table of guideline pruning. 2024.

582. WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, third edition. 2024. Website

583. World Health Organization. Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries: a WHO practical toolkit. 2019. Website

584. Dona D, Brigadoi G, Silva R, Liberati C, Zin A, Minotti C, et al. Impact of Antibiotic Treatment on Clinical Outcomes in COVID-19 Patients: A Systematic Review and Meta-Analysis. 2025.