

Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected

Interim guidance

12 January 2020

[WHO/nCoV/Clinical/2020.1](#)



Introduction

This is the first edition of this document for novel coronavirus, an adaptation of WHO Clinical management of severe acute respiratory infection when MERS-CoV infection is suspected publication (2019).

This document is intended for clinicians taking care of hospitalised adult and paediatric patients with severe acute respiratory infection (SARI) when a nCoV infection is suspected. It is not meant to replace clinical judgment or specialist consultation but rather to strengthen clinical management of these patients and provide to up-to-date guidance. Best practices for SARI including IPC and optimized supportive care for severely ill patients are essential.

This document is organized into the following sections:

1. Triage: recognize and sort patients with SARI
2. Immediate implementation of appropriate infection prevention and control (IPC) measures
3. Early supportive therapy and monitoring
4. Collection of specimens for laboratory diagnosis
5. Management of hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS)
6. Management of septic shock
7. Prevention of complications
8. Specific anti-nCoV treatments
9. Special considerations for pregnant patients

These symbols are used to flag interventions:

- ✔ Do: the intervention is beneficial (strong recommendation) **OR** the intervention is a best practice statement
- ✘ Don't: the intervention is known to be harmful.
- ⚠ Consider: the intervention may be beneficial in selected patients (conditional recommendation) **OR** be careful when considering this intervention.

This document aims to provide clinicians with updated interim guidance on timely, effective, and safe supportive management of patients with nCoV and SARI, particularly those with critical illness.

The recommendations in this document are derived from WHO publications.¹⁻⁴ Where WHO guidance is not available, we refer to evidence-based guidelines. Members of a WHO global network of clinicians, and clinicians who have treated SARS, MERS or severe influenza patients have reviewed the recommendations (see Acknowledgements). For queries, please email outbreak@who.int with 'nCoV clinical question' in the subject line.

1. Triage: early recognition of patients with SARI associated with nCoV infection

✓ **Triage: recognize and sort all patients with SARI at first point of contact with health care system (such as the emergency department). Consider nCoV as a possible etiology of SARI under certain conditions (see Table 1). Triage patients and start emergency treatments based on disease severity.**

Remarks: nCoV may present with mild, moderate, or severe illness; the latter includes severe pneumonia, ARDS, sepsis and septic shock. Early recognition of suspected patients allows for timely initiation of IPC (see Table 2). Early identification of those with severe manifestations (see Table 2) allows for immediate optimized supportive care treatments and safe, rapid admission (or referral) to intensive care unit according to institutional or national protocols. For those with mild illness, hospitalization may not be required unless there is concern for rapid deterioration. All patients discharged home should be instructed to return to hospital if they develop any worsening of illness.

Table 1. Definitions of patients with SARI, suspected of nCoV*

SARI	An ARI with history of fever or measured temperature $\geq 38\text{ C}^\circ$ and cough; onset within the last ~10 days; and requiring hospitalization. ⁵ However, the absence of fever does NOT exclude viral infection. ⁶
Surveillance case definitions for nCoV*	<ol style="list-style-type: none"> 1. Severe acute respiratory infection (SARI) in a person, with history of fever and cough requiring admission to hospital, with no other etiology that fully explains the clinical presentation¹ (clinicians should also be alert to the possibility of atypical presentations in patients who are immunocompromised); <p>AND any of the following:</p> <ol style="list-style-type: none"> a) A history of travel to Wuhan, Hubei Province China in the 14 days prior to symptom onset; or b) the disease occurs in a health care worker who has been working in an environment where patients with severe acute respiratory infections are being cared for, without regard to place of residence or history of travel; or c) the person develops an unusual or unexpected clinical course, especially sudden deterioration despite appropriate treatment, without regard to place of residence or history of travel, even if another etiology has been identified that fully explains the clinical presentation. 2. A person with acute respiratory illness of any degree of severity who, within 14 days before onset of illness, had any of the following exposures: <ol style="list-style-type: none"> a) close physical contact² with a confirmed case of nCoV infection, while that patient was symptomatic; or b) a healthcare facility in a country where hospital-associated nCoV infections have been reported;

*see <https://www.who.int/health-topics/coronavirus> for latest case definitions

¹ Testing should be according to local guidance for management of community-acquired pneumonia. Examples of other etiologies include *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, *Legionella pneumophila*, other recognized primary bacterial pneumonias, influenza viruses, and respiratory syncytial virus.

²Close contact² is defined as:

- Health care associated exposure, including providing direct care for nCoV patients, working with health care workers infected with nCoV, visiting patients or staying in the same close environment of a nCoV patient.
- Working together in close proximity or sharing the same classroom environment with a with nCoV patient
- Traveling together with nCoV patient in any kind of conveyance
- Living in the same household as a nCoV patient

The epidemiological link may have occurred within a 14-day period before or after the onset of illness in the case under consideration.

Table 2. Clinical syndromes associated with nCoV infection

Uncomplicated illness	Patients with uncomplicated upper respiratory tract viral infection, may have non-specific symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache, muscle pain or malaise. The elderly and immunosuppressed may present with atypical symptoms. These patients do not have any signs of dehydration, sepsis or shortness of breath.
Mild pneumonia	Patient with pneumonia and no signs of severe pneumonia. Child with non-severe pneumonia has cough or difficulty breathing + fast breathing: fast breathing (in breaths/min): <2 months, ≥ 60 ; 2–11 months, ≥ 50 ; 1–5 years, ≥ 40 and no signs of severe pneumonia.
Severe pneumonia	Adolescent or adult: fever or suspected respiratory infection, plus one of respiratory rate >30 breaths/min, severe respiratory distress, or $SpO_2 < 90\%$ on room air (adapted from [1]). Child with cough or difficulty in breathing, plus at least one of the following: central cyanosis or $SpO_2 < 90\%$; severe respiratory distress (e.g. grunting, very severe chest indrawing); signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. Other signs of pneumonia may be present: chest indrawing, fast breathing (in breaths/min): <2 months, ≥ 60 ; 2–11 months, ≥ 50 ; 1–5 years, ≥ 40 . ² The diagnosis is clinical; chest imaging can exclude complications.
Acute Respiratory Distress Syndrome⁷⁻⁹	Onset: new or worsening respiratory symptoms within one week of known clinical insult. Chest imaging (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules. Origin of oedema: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of oedema if no risk factor present. Oxygenation (adults): <ul style="list-style-type: none"> Mild ARDS: $200 \text{ mmHg} < PaO_2/FiO_2 \leq 300 \text{ mmHg}$ (with PEEP or CPAP $\geq 5 \text{ cmH}_2\text{O}$,⁷ or non-ventilated⁸) Moderate ARDS: $100 \text{ mmHg} < PaO_2/FiO_2 \leq 200 \text{ mmHg}$ with PEEP $\geq 5 \text{ cmH}_2\text{O}$,⁷ or non-ventilated⁸) Severe ARDS: $PaO_2/FiO_2 \leq 100 \text{ mmHg}$ with PEEP $\geq 5 \text{ cmH}_2\text{O}$,⁷ or non-ventilated⁸) When PaO_2 is not available, $SpO_2/FiO_2 \leq 315$ suggests ARDS (including in non-ventilated patients) Oxygenation (children; note OI = Oxygenation Index and OSI = Oxygenation Index using SpO_2): <ul style="list-style-type: none"> Bilevel NIV or CPAP $\geq 5 \text{ cmH}_2\text{O}$ via full face mask: $PaO_2/FiO_2 \leq 300 \text{ mmHg}$ or $SpO_2/FiO_2 \leq 264$ Mild ARDS (invasively ventilated): $4 \leq OI < 8$ or $5 \leq OSI < 7.5$ Moderate ARDS (invasively ventilated): $8 \leq OI < 16$ or $7.5 \leq OSI < 12.3$ Severe ARDS (invasively ventilated): $OI \geq 16$ or $OSI \geq 12.3$
Sepsis^{10,11}	Adults: life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection, with organ dysfunction*. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia. Children: suspected or proven infection and ≥ 2 SIRS criteria, of which one must be abnormal temperature or white blood cell count.
Septic shock^{10,12}	Adults: persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP $\geq 65 \text{ mmHg}$ and serum lactate level $> 2 \text{ mmol/L}$. Children (based on [12]): any hypotension (SBP $< 5^{\text{th}}$ centile or $> 2 \text{ SD}$ below normal for age) or 2-3 of the following: altered mental state; tachycardia or bradycardia (HR $< 90 \text{ bpm}$ or $> 160 \text{ bpm}$ in infants and HR $< 70 \text{ bpm}$ or $> 150 \text{ bpm}$ in children); prolonged capillary refill ($> 2 \text{ sec}$) or warm vasodilation with bounding pulses; tachypnea; mottled skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia.

Abbreviations: ARI, acute respiratory infection; BP, blood pressure; bpm, beats/minute; CPAP, continuous positive airway pressure; FiO_2 , fraction of inspired oxygen; MAP, mean arterial pressure; NIV, noninvasive ventilation; OI, Oxygenation Index; OSI, Oxygenation Index using SpO_2 ; PaO_2 , partial pressure of oxygen; PEEP, positive end-expiratory pressure; SBP, systolic blood pressure; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SpO_2 , oxygen saturation. *If altitude is higher than 1000m, then correction factor should be calculated as follows: $PaO_2/FiO_2 \times \text{Barometric pressure}/760$.

* The SOFA score ranges from 0 to 24 and includes points related to 6 organ systems: respiratory (hypoxemia defined by low PaO_2/FiO_2), coagulation (low platelets), liver (high bilirubin), cardiovascular (hypotension), central nervous system (low level of consciousness defined by Glasgow Coma Scale), and renal (low urine output or high creatinine). Sepsis is defined by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score¹³ of ≥ 2 points. Assume the baseline score is zero if data are not available

2. Immediate implementation of appropriate IPC measures

IPC is a critical and integral part of clinical management of patients and should be initiated at the point of entry of the patient to hospital (typically the Emergency Department). Standard precautions should always be routinely applied in all areas of health care facilities. Standard precautions include hand hygiene; use of PPE to avoid direct contact with patients' blood, body fluids, secretions (including respiratory secretions) and non-intact skin. Standard precautions also include prevention of needle-stick or sharps injury; safe waste management; cleaning and disinfection of equipment; and cleaning of the environment.

Table 2. How to implement infection prevention and control measures for patients with suspected or confirmed nCoV infection ^{14,15}

At triage	Give suspect patient a medical mask and direct patient to separate area, an isolation room if available. Keep at least 1meter distance between suspected patients and other patients. Instruct all patients to cover nose and mouth during coughing or sneezing with tissue or flexed elbow for others. Perform hand hygiene after contact with respiratory secretions
Apply droplet precautions	Droplet precautions prevent large droplet transmission of respiratory viruses. Use a medical mask if working within 1-2 metre s of the patient. Place patients in single rooms, or group together those with the same etiological diagnosis. If an etiological diagnosis is not possible, group patients with similar clinical diagnosis and based on epidemiological risk factors, with a spatial separation. When providing care in close contact with a patient with respiratory symptoms (e.g. coughing or sneezing), use eye protection (face-mask or goggles), because sprays of secretions may occur. Limit patient movement within the institution and ensure that patients wear medical masks when outside their rooms.
Apply contact precautions	Droplet and contact precautions prevent direct or indirect transmission from contact with contaminated surfaces or equipment (i.e. contact with contaminated oxygen tubing/interfaces). Use PPE (medical mask, eye protection, gloves and gown) when entering room and remove PPE when leaving. If possible, use either disposable or dedicated equipment (e.g. stethoscopes, blood pressure cuffs and thermometers). If equipment needs to be shared among patients, clean and disinfect between each patient use. Ensure that health care workers refrain from touching their eyes, nose, and mouth with potentially contaminated gloved or ungloved hands. Avoid contaminating environmental surfaces that are not directly related to patient care (e.g. door handles and light switches). Ensure adequate room ventilation. Avoid movement of patients or transport. Perform hand hygiene.
Apply airborne precautions when performing an aerosol generating procedure	Ensure that healthcare workers performing aerosol-generating procedures (i.e. open suctioning of respiratory tract, intubation, bronchoscopy, cardiopulmonary resuscitation) use PPE, including gloves, long-sleeved gowns, eye protection, and fit-tested particulate respirators (N95 or equivalent, or higher level of protection). (The scheduled fit test should not be confused with user seal check before each use.) Whenever possible, use adequately ventilated single rooms when performing aerosol-generating procedures, meaning negative pressure rooms with minimum of 12 air changes per hour or at least 160 litres/second/patient in facilities with natural ventilation. Avoid the presence of unnecessary individuals in the room. Care for the patient in the same type of room after mechanical ventilation commences.

Abbreviations: ARI, acute respiratory infection; PPE, personal protective equipment

3. Early supportive therapy and monitoring

✔ Give supplemental oxygen therapy immediately to patients with SARI and respiratory distress, hypoxaemia, or shock.

Remarks: Initiate oxygen therapy at 5 L/min and titrate flow rates to reach target SpO₂ ≥90% in non-pregnant adults and SpO₂ ≥92-95 % in pregnant patients.^{1,2} Children with emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma or convulsions) should receive oxygen therapy during resuscitation to target SpO₂ ≥94%; otherwise, the target SpO₂ is ≥90%.⁴ All areas where patients with SARI are cared for should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (nasal cannula, simple face mask, and mask with reservoir bag). Use contact precautions when handling contaminated oxygen interfaces of patients with nCoV infection.

✔ Use conservative fluid management in patients with SARI when there is no evidence of shock.

Remarks: Patients with SARI should be treated cautiously with intravenous fluids, because aggressive fluid resuscitation may worsen oxygenation, especially in settings where there is limited availability of mechanical ventilation.¹⁶

✔ Give empiric antimicrobials to treat all likely pathogens causing SARI. Give antimicrobials within one hour of initial patient assessment for patients with sepsis.

Remarks: Although the patient may be suspected to have nCoV, administer appropriate empiric antimicrobials within **ONE hour** of identification of sepsis.¹⁷ Empiric antibiotic treatment should be based on the clinical diagnosis (community-acquired pneumonia, health care-associated pneumonia [if infection was acquired in healthcare setting], or sepsis), local epidemiology and susceptibility data, and treatment guidelines. Empiric therapy includes a neuraminidase inhibitor for treatment of influenza when there is local circulation or other risk factors, including travel history or exposure to animal influenza viruses.¹⁸ Empiric therapy should be de-escalated on the basis of microbiology results and clinical judgment.

✘ Do not routinely give systemic corticosteroids for treatment of viral pneumonia or ARDS outside of clinical trials unless they are indicated for another reason.

Remarks: A systematic review of observational studies of corticosteroids administered to patients with SARS reported no survival benefit and possible harms (avascular necrosis, psychosis, diabetes, and delayed viral clearance).¹⁹ A systematic review of observational studies in influenza found a higher risk of mortality and secondary infections with corticosteroids; the evidence was judged as very low to low quality due to confounding by indication.²⁰ A subsequent study that addressed this limitation by adjusting for time-varying confounders found no effect on mortality.²¹ Finally, a recent study of patients receiving corticosteroids for MERS used a similar statistical approach and found no effect of corticosteroids on mortality but delayed lower respiratory

tract (LRT) clearance of MERS-CoV.²² Given lack of effectiveness and possible harm, routine corticosteroids should be avoided unless they are indicated for another reason. See section 6 for the use of corticosteroids in sepsis.

- ✔ **Closely monitor patients with SARI for signs of clinical deterioration, such as rapidly progressive respiratory failure and sepsis, and apply supportive care interventions immediately.**

Remarks: Application of timely, effective, and safe supportive therapies is the cornerstone of therapy for patients that develop severe manifestations of nCoV.

- ✔ **Understand the patient's co-morbid condition(s) to tailor the management of critical illness and appreciate the prognosis. Communicate early with patient and family.**

Remarks: During intensive care management of SARI, determine which chronic therapies should be continued and which therapies should be stopped temporarily. Communicate proactively with patients and families and provide support and prognostic information. Understand the patient's values and preferences regarding life-sustaining interventions.

4. Collection of specimens for laboratory diagnosis

WHO guidance on specimen collection, processing, and laboratory testing, including related biosafety procedures, is available.²³

- ✔ **Collect blood cultures for bacteria that cause pneumonia and sepsis, ideally before antimicrobial therapy. DO NOT delay antimicrobial therapy to collect blood cultures.**
- ✔ **Collect specimens from BOTH the upper respiratory tract (URT; nasopharyngeal and oropharyngeal) AND lower respiratory tract (LRT; expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage) for nCoV testing by RT-PCR. Clinicians may elect to collect only LRT samples when these are readily available (for example, in mechanically ventilated patients).**
- ✔ **Serology for diagnostic purposes is recommended only when RT-PCR is not available.²³**

Remarks: Use appropriate PPE for specimen collection (droplet and contact precautions for URT specimens; airborne precautions for LRT specimens). When collecting URT samples, use viral swabs (sterile Dacron or rayon, not cotton) and viral transport media. Do not sample the nostrils or tonsils. In a patient with suspected novel coronavirus, especially with pneumonia or severe illness, a single URT sample does not exclude the diagnosis, and additional URT and LRT samples are recommended.²³ LRT (vs. URT) samples are more likely to be positive and for a longer period.²³ Clinicians may elect to collect only LRT samples when these are readily available (for example, in mechanically ventilated patients). Sputum induction should be avoided due to increased risk of increasing aerosol transmission.

Remarks: Dual infections with other respiratory viral infections have been found in SARS and MERS cases. At this stage we need detailed microbiologic studies in all suspected cases. Both URT and LRT specimens can be tested for other respiratory viruses, such as influenza A and B (including zoonotic influenza A), respiratory syncytial virus, parainfluenza viruses, rhinoviruses, adenoviruses, enteroviruses (e.g. EVD68), human metapneumovirus, and endemic human coronaviruses (i.e. HKU1, OC43, NL63, and 229E). LRT specimens can also be tested for bacterial pathogens, including *Legionella pneumophila*.

- ✔ **In hospitalized patients with confirmed nCoV infection, repeat URT and LRT samples should be collected to demonstrate viral clearance. The frequency of specimen collection will depend on local circumstances but should be at least every 2 to 4 days until there are two consecutive negative results (both URT and LRT samples if both are collected) in a clinically recovered patient at least 24 hours apart. If local infection control practice requires two negative results before removal of droplet precautions, specimens may be collected as often as daily.**

5. Management of hypoxemic respiratory failure and ARDS

- ✔ **Recognize severe hypoxemic respiratory failure when a patient with respiratory distress is failing standard oxygen therapy.**

Remarks: Patients may continue to have increased work of breathing or hypoxemia even when oxygen is delivered via a face mask with reservoir bag (flow rates of 10-15 L/min, which is typically the minimum flow required to maintain bag inflation; FiO₂ 0.60-0.95). Hypoxemic respiratory failure in ARDS commonly results from intrapulmonary ventilation-perfusion mismatch or shunt and usually requires mechanical ventilation.

- ! **High-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV) should only be used in selected patients with hypoxemic respiratory failure. The risk of treatment failure is high in patients with MERS treated with NIV, and patients treated with either HFNO or NIV should be closely monitored for clinical deterioration.**

Remark 1: HFNO systems can deliver 60 L/min of gas flow and FiO₂ up to 1.0; paediatric circuits generally only handle up to 15 L/min, and many children will require an adult circuit to deliver adequate flow. Compared to standard oxygen therapy, HFNO reduces the need for intubation.²⁴ Patients with hypercapnia (exacerbation of obstructive lung disease, cardiogenic pulmonary oedema), hemodynamic instability, multi-organ failure, or abnormal mental status should generally not receive HFNO, although emerging data suggest that HFNO may be safe in patients with mild-moderate and non-worsening hypercapnia.²⁵ Patients receiving HFNO should be in a monitored setting and cared for by experienced personnel capable of endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 1 hr). Evidence-based guidelines on HFNO do not exist, and reports on HFNO in MERS patients are limited.²⁶

Remark 2: NIV guidelines make no recommendation on use in hypoxemic respiratory failure (apart from cardiogenic pulmonary oedema and post-operative respiratory failure) or pandemic viral illness (referring to studies of SARS and pandemic influenza).²⁷ Risks include delayed intubation, large tidal volumes, and injurious transpulmonary pressures. Limited data suggest a high failure rate when MERS patients receive NIV.²⁸ Patients receiving a trial of NIV should be in a monitored setting and cared for by experienced personnel capable of endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 1 hr). Patients with hemodynamic instability, multiorgan failure, or abnormal mental status should not receive NIV.

Remark 3: Recent publications suggest that newer HFNO and NIV systems with good interface fitting do not create widespread dispersion of exhaled air and therefore should be associated with low risk of airborne transmission.²⁹⁻³¹



Endotracheal intubation should be performed by a trained and experienced provider using airborne precautions.

Remarks: Patients with ARDS, especially young children or those who are obese or pregnant, may desaturate quickly during intubation. Pre-oxygenate with 100% FiO₂ for 5 minutes, via a face mask with reservoir bag, bag-valve mask, HFNO, or NIV. Rapid sequence intubation is appropriate after an airway assessment that identifies no signs of difficult intubation³².

The following recommendations in this section pertain to mechanically ventilated patients with ARDS.^{17,33} These focus on adults; consensus-based recommendations for children are available.³⁴



Implement mechanical ventilation using lower tidal volumes (4–8 ml/kg predicted body weight, PBW) and lower inspiratory pressures (plateau pressure <30 cmH₂O).

Remarks: This is a strong recommendation from a clinical guideline for patients with ARDS,³³ and is suggested for patients with sepsis-induced respiratory failure who do not meet ARDS criteria.¹⁷ The initial 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). Hypercapnia is permitted if meeting the pH goal of 7.30–7.45. Ventilator protocols are available.³⁵ The use of deep sedation may be required to control respiratory drive and achieve tidal volume targets. Although high driving pressure (plateau pressure–PEEP) may more accurately predict increased mortality in ARDS compared to high tidal volume or plateau pressure,³⁶ RCTs of ventilation strategies that target driving pressure are not currently available.



In patients with severe ARDS, prone ventilation for >12 hours per day is recommended.

Remarks: Application of prone ventilation is strongly recommended for adult and paediatric patients with severe ARDS³³ but requires sufficient human resources and expertise to be performed safely.^{37,38}



Use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion.

Remarks: This is a strong guideline recommendation,¹⁷ the main effect is to shorten the duration of ventilation. See reference [39] for details of a sample protocol.



In patients with moderate or severe ARDS, higher PEEP instead of lower PEEP is suggested.

Remarks: 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 FiO₂ required to maintain SpO₂.³⁵ A related intervention of recruitment manoeuvres (RMs) is delivered as episodic periods of high continuous positive airway pressure [30–40 cm H₂O], 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.³³ For PEEP, the guideline considered an individual patient data meta-analysis⁴⁰ of 3 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.⁴¹ 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, is suggested.⁴²



In patients with moderate-severe ARDS (PaO₂/FiO₂ <150), neuromuscular blockade by continuous infusion should not be routinely used.

Remarks: One trial found that this strategy improved survival in patients with severe ARDS (PaO₂/FiO₂ <150) without causing significant weakness,⁴³ but results of a recent larger trial found that use of neuromuscular blockade with high PEEP strategy was not associated with survival when compared to a light sedation strategy without neuromuscular blockade⁴⁴. Continuous neuromuscular blockade may still be considered in patients with ARDS in certain situations: ventilator dyssynchrony despite sedation, such that tidal volume limitation cannot be reliably achieved; or refractory hypoxemia or hypercapnia.



In settings with access to expertise in extracorporeal life support (ECLS), consider referral of patients with refractory hypoxemia despite lung protective ventilation.

Remarks: A recent guideline made no recommendation about ECLS in patients with ARDS.³³ Since then, an RCT of ECLS for patients with ARDS was stopped early and found no statistically significant difference in the primary outcome of 60-day mortality between ECLS and standard medical management (including prone positioning and neuromuscular blockade).⁴⁵ However, ECLS was associated with a reduced risk of the composite outcome of mortality and crossover to ECLS,⁴⁵ and a *post hoc* Bayesian analysis of this RCT showed that ECLS is very likely to reduce mortality across a range of prior assumptions.⁴⁶ In patients with MERS-CoV infection, ECLS vs. conventional treatment was associated with reduced mortality in a cohort study.⁴⁷ ECLS should

only be offered in expert centres with a sufficient case volume to maintain expertise and that can apply the IPC measures required for nCoV patients.⁴⁸

- ✗ **Avoid disconnecting the patient from the ventilator, which results in loss of PEEP and atelectasis. Use in-line catheters for airway suctioning and clamp endotracheal tube when disconnection is required (for example, transfer to a transport ventilator).**

6. Management of septic shock

- ✓ **Recognize septic shock in adults when infection is suspected or confirmed AND vasopressors are needed to maintain mean arterial pressure (MAP) ≥ 65 mmHg AND lactate is ≥ 2 mmol/L, in absence of hypovolemia. Recognize septic shock in children with any hypotension (systolic blood pressure [SBP] $< 5^{\text{th}}$ centile or > 2 SD below normal for age) or 2-3 of the following: altered mental state; tachycardia or bradycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or warm vasodilation with bounding pulses; tachypnea; mottled skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia.**

Remarks: In the absence of a lactate measurement, use MAP and clinical signs of perfusion to define shock. Standard care includes early recognition and the following treatments within 1 hour of recognition: antimicrobial therapy and fluid loading and vasopressors for hypotension.⁴⁹ The use of central venous and arterial catheters should be based on resource availability and individual patient needs. Detailed guidelines are available for the management of septic shock in adults¹⁷ and children.^{2,3,12}

- ✓ **In resuscitation from septic shock in adults, give at least 30 ml/kg of isotonic crystalloid in adults in the first 3 hours. In resuscitation from septic shock in children in well-resourced settings, give 20 ml/kg as a rapid bolus and up to 40-60 ml/kg in the first 1 hr.**
- ✗ **Do not use hypotonic crystalloids, starches, or gelatins for resuscitation.**
- ! **Fluid resuscitation may lead to volume overload, including respiratory failure. If there is no response to fluid loading and signs of volume overload appear (for example, jugular venous distension, crackles on lung auscultation, pulmonary oedema on imaging, or hepatomegaly in children), then reduce or discontinue fluid administration. This step is particularly important where mechanical ventilation is not available. Alternate fluid regimens are suggested when caring for children in resource-limited settings⁵⁰**

Remarks: Crystalloids include normal saline and Ringer's lactate. Determine need for additional fluid boluses (250-1000 ml in adults or 10-20 ml/kg in children) based on clinical response and improvement of perfusion targets. Perfusion targets include MAP (> 65 mmHg or age-appropriate targets in children), urine output (> 0.5 ml/kg/hr in adults, 1 ml/kg/hr in children), and improvement of skin mottling, capillary refill, level of consciousness, and lactate. Consider dynamic indices of volume responsiveness to guide volume administration beyond initial resuscitation based on local resources and experience.¹⁷ These indices include passive leg raises, fluid challenges with serial stroke volume measurements, or variations in systolic pressure, pulse pressure, inferior vena cava size, or stroke volume in response to changes in intrathoracic pressure during mechanical ventilation.

Starches are associated with an increased risk of death and acute kidney injury vs. crystalloids. The effects of gelatins are less clear, but they are more expensive than crystalloids.^{51,52} Hypotonic (vs. isotonic) solutions are less effective at increasing intravascular volume. Surviving Sepsis also suggests albumin for resuscitation when patients require substantial amounts of crystalloids, but this conditional recommendation is based on low-quality evidence.¹⁷

- ✓ **Administer vasopressors when shock persists during or after fluid resuscitation. The initial blood pressure target is MAP ≥ 65 mmHg in adults and age-appropriate targets in children.**
- ! **If central venous catheters are not available, vasopressors can be given through a peripheral IV, but use a large vein and closely monitor for signs of extravasation and local tissue necrosis. If extravasation occurs, stop infusion. Vasopressors can also be administered through intraosseous needles.**
- ! **If signs of poor perfusion and cardiac dysfunction persist despite achieving MAP target with fluids and vasopressors, consider an inotrope such as dobutamine.**

Remarks: Vasopressors (i.e. norepinephrine, epinephrine, vasopressin, and dopamine) are most safely given through a central venous catheter at a strictly controlled rate, but it is also possible to safely administer them via peripheral vein⁵³ and intraosseous needle. Monitor blood pressure frequently and titrate the vasopressor to the minimum dose necessary to maintain perfusion and prevent side effects. Norepinephrine is considered first-line in adult patients; epinephrine or vasopressin can be added to achieve the MAP target. Because of the risk of tachyarrhythmia, reserve dopamine for selected patients with low risk of tachyarrhythmia or those with bradycardia. In children with cold shock (more common), epinephrine is considered first-line, while norepinephrine is used in patients with warm shock (less common).

No RCTs have compared dobutamine to placebo for clinical outcomes.¹⁷

7. Prevention of complications

Implement the following interventions (Table 3) to prevent complications associated with critical illness. These interventions are based on Surviving Sepsis¹⁷ or other guidelines,⁵⁴⁻⁵⁷ and are generally limited to feasible recommendations based on high quality evidence.

Table 3. Prevention of complications

Anticipated Outcome	Interventions
Reduce days of invasive mechanical ventilation	<ul style="list-style-type: none"> • 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
Reduce incidence of ventilator-associated pneumonia	<ul style="list-style-type: none"> • Oral intubation is preferable to nasal intubation in adolescents and adults • Keep patient in semi-recumbent position (head of bed elevation 30-45°) • 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 venous thromboembolism	<ul style="list-style-type: none"> • Use pharmacological prophylaxis (low molecular-weight heparin [preferred if available] or heparin 5000 units subcutaneously twice daily) in adolescents and adults without contraindications. For those with contraindications, use mechanical prophylaxis (intermittent pneumatic compression devices).
Reduce incidence of catheter-related bloodstream infection	<ul style="list-style-type: none"> • Use a checklist with completion verified by a real-time observer as 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	<ul style="list-style-type: none"> • Turn patient every two hours
Reduce incidence of stress ulcers and gastrointestinal bleeding	<ul style="list-style-type: none"> • 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 gastrointestinal bleeding include mechanical ventilation for ≥48 hours, coagulopathy, renal replacement therapy, liver disease, multiple comorbidities, and higher organ failure score
Reduce incidence of ICU-related weakness	<ul style="list-style-type: none"> • Actively mobilize the patient early in the course of illness when safe to do so

8. Specific anti-Novel-CoV treatments and clinical research

! There is no current evidence from RCTs to recommend any specific anti-nCoV treatment for patients with suspected or confirmed nCoV.

✓ Unlicensed treatments should be administered only in the context of ethically-approved clinical trials or the Monitored Emergency Use of Unregistered Interventions Framework (MEURI), with strict monitoring.

<https://www.who.int/ethics/publications/infectious-disease-outbreaks/en/>

✓ Clinical characterization protocols are available, including the SPRINT-SARI <https://isaric.tghn.org/sprint-sari/> and WHO-ISARIC forms available at <https://isaric.tghn.org/protocols/severe-acute-respiratory-infection-data-tools/>. Contact oubreak@who.int for additional questions.

9. Special considerations for pregnant patients

✓ Pregnant women with suspected or confirmed nCoV should be treated with supportive therapies as described above, taking into account the physiologic adaptations of pregnancy.

✓ The use of investigational therapeutic agents outside of a research study should be guided by individual risk-benefit analysis based on potential benefit for mother and safety to fetus, with consultation from an obstetric specialist and ethics committee.

✓ Emergency delivery and pregnancy termination decisions are challenging and based on many factors: gestational age, maternal condition, and fetal stability. Consultations with obstetric, neonatal, and intensive care specialists (depending on the condition of the mother) are essential.

10. Acknowledgements

The original version of this document was developed in consultation with International Forum for Acute Care Trialists (InFACT), ISARIC and Surviving Sepsis Campaign. The following individuals contributed to or reviewed the current version. Confidentiality and declarations of interest were collected and reviewed.

WHO: April Baller, Janet Diaz, Dina Pfeifer, Maria Van Kerkhove, Satoko Otsu, Richard Peabody.

Non-WHO experts: Neill Adhikari, Sunnybrook Health Sciences Centre and University of Toronto; Yaseen Arabi, King Saud Bin Abdulaziz University for Health Sciences, Saudi Arabia; Kenneth Baillie, University of Edinburgh, UK; Gail Carson University of Oxford, ISARIC; Charles David Gomersall The Chinese University of Hong Kong; Jake Dunning, Public Health England, UK; Rob Fowler, University of Toronto, Canada; Susan Gerber, Centers for Disease Control and Prevention, USA; Frederick Hayden, University of Virginia, USA; Peter Horby University of Oxford, ISARIC; David Hui, Chinese University of Hong Kong, Hong Kong SAR; Yae-Jean Kim, Sungkyunkwan University, Samsung Medical Center, Korea; Srinivas Murthy, University of British Columbia, Canada; Norio Ohmagari, M.D., M.Sc., Ph.D, WHO Collaborating Centre for Prevention, Preparedness and Response to Emerging Infectious Diseases, National Center for Global Health and Medicine Hospital Toyama, Tokyo Japan; Yinzhong Shen Shanghai Public Health Clinical Center, Fudan University Naoki Shimizu; Tim Uyeki, Centers for Disease Control and Prevention, USA.

References

1. Rosjo H, Varpula M, Hagve TA, et al. Circulating high sensitivity troponin T in severe sepsis and septic shock: distribution, associated factors, and relation to outcome. *Intensive Care Med* 2011;37:77-85.
2. Pocket book of hospital care for children: Guidelines for the management of common childhood illnesses [http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/]. 2nd ed. Geneva: WHO; 2013.
3. Gunnerson KJ, Shaw AD, Chawla LS, et al. TIMP2*IGFBP7 biomarker panel accurately predicts acute kidney injury in high-risk surgical patients. *J Trauma Acute Care Surg* 2016;80:243-9.
4. Oxygen therapy for children: a manual for health workers [http://www.who.int/maternal_child_adolescent/documents/child-oxygen-therapy/en/]. Geneva: WHO; 2016.
5. Global Epidemiological Surveillance Standards for Influenza [http://www.who.int/influenza/resources/documents/influenza_surveillance_manual/en/]. Geneva: WHO; 2014.
6. Shalhoub S, Farahat F, Al-Jiffri A, et al. IFN-alpha2a or IFN-beta1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *J Antimicrob Chemother* 2015;70:2129-32.
7. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526-33.
8. Riviello ED, Kiviri W, Twagirumugabe T, et al. Hospital Incidence and Outcomes of the Acute Respiratory Distress Syndrome Using the Kigali Modification of the Berlin Definition. *Am J Respir Crit Care Med* 2016;193:52-9.
9. Khemani RG, Smith LS, Zimmerman JJ, Erickson S, Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology: proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med* 2015;16:S23-40.
10. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801-10.
11. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005;6:2-8.
12. Davis AL, Carcillo JA, Aneja RK, et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. *Crit Care Med* 2017;45:1061-93.
13. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22:707-10.
14. Infection prevention and control of epidemic-and pandemic prone acute respiratory infections in health care [http://www.who.int/csr/bioriskreduction/infection_control/publication/en/]. Geneva: WHO; 2014.
15. Infection prevention and control during health care for probable or confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection: Interim guidance. Geneva: WHO; 2015.
16. Schultz MJ, Dunser MW, Dondorp AM, et al. Current challenges in the management of sepsis in ICUs in resource-poor settings and suggestions for the future. *Intensive Care Med* 2017;43:612-24.
17. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017;43:304-77.
18. Clinical management of human infection with pandemic (H1N1) 2009: revised guidance [http://www.who.int/csr/resources/publications/swineflu/clinical_management/en/]. Geneva: WHO; 2009.
19. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med* 2006;3:e343.
20. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev* 2016;3:CD010406.
21. Delaney JW, Pinto R, Long J, et al. The influence of corticosteroid treatment on the outcome of influenza A(H1N1pdm09)-related critical illness. *Crit Care* 2016;20:75.
22. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. *Am J Respir Crit Care Med* 2018;197:757-67.
23. Laboratory testing for Middle East Respiratory Syndrome Coronavirus: Interim guidance [http://www.who.int/csr/disease/coronavirus_infections/mers-laboratory-testing/en/]. Geneva: WHO; 2018.
24. Ou X, Hua Y, Liu J, Gong C, Zhao W. Effect of high-flow nasal cannula oxygen therapy in adults with acute hypoxemic respiratory failure: a meta-analysis of randomized controlled trials. *CMAJ* 2017;189:E260-E7.
25. Lee MK, Choi J, Park B, et al. High flow nasal cannulae oxygen therapy in acute-moderate hypercapnic respiratory failure. *Clin Respir J* 2018;12:2046-56.
26. Luo Y, Ou R, Ling Y, Qin T. The therapeutic effect of high flow nasal cannula oxygen therapy for the first imported case of Middle East respiratory syndrome to China [Chinese]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2015;27:841-4.

27. Rochweg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J* 2017;50.
28. Arabi YM, Arifi AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Ann Intern Med* 2014;160:389-97.
29. Leung CCH, Joynt GM, Gomersall CD, et al. Comparison of high-flow nasal cannula versus oxygen face mask for environmental bacterial contamination in critically ill pneumonia patients: a randomized controlled crossover trial. *J Hosp Infect* 2019;101:84-7.
30. Hui DS, Chow BK, Lo T, et al. Exhaled air dispersion during high-flow nasal cannula therapy versus CPAP via different masks. *Eur Respir J* 2019;53.
31. Hui DS, Chow BK, Lo T, et al. Exhaled air dispersion during noninvasive ventilation via helmets and a total facemask. *Chest* 2015;147:1336-43.
32. Detsky ME, Jivraj N, Adhikari NK, et al. Will This Patient Be Difficult to Intubate?: The Rational Clinical Examination Systematic Review. *JAMA* 2019;321:493-503.
33. Fan E, Del Sorbo L, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2017;195:1253-63.
34. 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:S51-60.
35. ARDS Network Tools. 2014. (Accessed 25 July, 2018, at <http://www.ardsnet.org/tools.shtml>.)
36. Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015;372:747-55.
37. Messerole E, Peine P, Wittkopp S, Marini JJ, Albert RK. The pragmatics of prone positioning. *Am J Respir Crit Care Med* 2002;165:1359-63.
38. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159-68.
39. National Heart L, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network,, Wiedemann HP, Wheeler AP, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354:2564-75.
40. Briel M, Meade M, Mercat A, 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* 2010;303:865-73.
41. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial Investigators, Cavalcanti AB, Suzumura EA, 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;318:1335-45.
42. Goligher EC, Kavanagh BP, Rubenfeld GD, 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;190:70-6.
43. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010;363:1107-16.
44. National Heart L, Blood Institute PCTN, Moss M, et al. Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome. *N Engl J Med* 2019;380:1997-2008.
45. Combes A, Hajage D, Capellier G, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. *N Engl J Med* 2018;378:1965-75.
46. Goligher EC, Tomlinson G, Hajage D, 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;320:2251-9.
47. Alshahrani MS, Sindi A, Alshamsi F, et al. Extracorporeal membrane oxygenation for severe Middle East respiratory syndrome coronavirus. *Ann Intensive Care* 2018;8:3.
48. Combes A, Brodie D, Bartlett R, 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;190:488-96.
49. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. *Intensive Care Med* 2018;44:925-8.
50. Lamontagne F, Meade MO, Hebert PC, et al. Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial. *Intensive Care Med* 2016;42:542-50.
51. Rochweg B, Alhazzani W, Gibson A, et al. Fluid type and the use of renal replacement therapy in sepsis: a systematic review and network meta-analysis. *Intensive Care Med* 2015;41:1561-71.
52. Rochweg B, Alhazzani W, Sindi A, et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. *Ann Intern Med* 2014;161:347-55.
53. 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. *J Crit Care* 2015;30:653 e9-17.
54. Schmidt GA, Girard TD, Kress JP, 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. *Am J Respir Crit Care Med* 2017;195:115-9.
55. Muscedere J, Dodek P, Keenan S, et al. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: prevention. *J Crit Care* 2008;23:126-37.
56. Klompas M, Branson R, Eichenwald EC, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol* 2014;35:915-36.
57. Marschall J, Mermel LA, Fakih M, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol* 2014;35:753-71.

© World Health Organization 2020. All rights reserved.

This is a draft. The content of this document is not final, and the text may be subject to revisions before publication. The document may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means without the permission of the World Health Organization.