The endTB COVID-19 Response

Interim Guidance for the endTB Trial sites

Version 1.3

Updated 24 November 2020

Notice

This guide is a draft version designed to give guidance to the endTB Project sites on the response to the COVID-19 outbreak. It is intended to be a resource for physicians and other health care professionals. Every effort possible has been made to ensure that the material presented here is accurate, reliable, and in accordance with current standards. However, as new research and experience expand our knowledge, recommendations for care and treatment are expected to change. Furthermore, this guide has not been field tested and is based on limited global experience on the COVID-19 response. It is therefore the responsibility of the individual physician or other health care professional to use their best medical judgment in determining appropriate patient care or treatment.

This guide is provided as a resource that can be adapted to your local context. The use of this guide is under your responsibility; there is no warranty that the information contained herein is complete or free from error. By choosing to use this guide, you acknowledge and agree to the terms of this disclaimer.

This guide will be regularly updated and enriched. New versions will be posted at www.endTB.org.

Table of Contents

Acknowledgements

endTB is supported by Unitaid. Unitaid is a unique funding mechanism engaged in finding new ways to prevent, treat and diagnose HIV/AIDS, tuberculosis and malaria more quickly, more cheaply and more effectively.

Website: www.unitaid.eu

Writing Team:

Lorenzo Guglielmetti
Uzma Khan
Carole Mitnick
Michael L. Rich
Francis Varaine
Gustavo E. Velásquez

Abbreviations

Ab	Antibody
Ag	Antigen
ARDS	Acute respiratory distress syndrome
BP	Blood pressure
C	Celsius
CDC USA	Centers for Disease Control and Prevention USA
CHW	Community health worker
COVID-19	Coronavirus disease 2019
DTT	Dithiothreitol
FiO2	Fraction of inspired oxygen
HCW	Healthcare worker
HIV	Human immunodeficiency virus
ICU	Intensive care unit
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IPC	Infection prevention and control
IV	Intravenous
L/min	Liters per minute
MDR-TB	Multidrug-resistant tuberculosis
MoH	Ministry of Health
MSF	Médecins Sans Frontières
NPV	Negative predictive value
O2	Oxygen saturation
PAHO	Pan-American Health Organization
PaO2	Partial pressure of oxygen
PI	Principal Investigator
PIH	Partners In Health
PO	Per os
POC	Point of care
PPE	Personal protective equipment
PPV	Positive predictive value
RDT	Rapid diagnostic test
RR	Respiratory rate
RT-PCR	Reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SOP	Standard Operating Procedure
SRA	Stringent regulatory authority
T	Temperature
TB	Tuberculosis
UN	United Nations
WHO	World Health Organization
µL	Microliter

1. Synopsis of management of COVID-19 in the endTB trial

a. Statement of the problem

- Coronavirus disease 2019 (COVID-19), is an infectious disease caused by the novel SARS-CoV-2 coronavirus that can cause an acute and severe respiratory illness.
- COVID-19 is an emerging disease; the global population has no known immunity to SARS-CoV-2, it therefore causes high morbidity and mortality.
- The World Health Organization (WHO) declared that COVID-19 was a global pandemic on March 11, 2020.
- Participants and patients being screened for the endTB and endTB-Q clinical trials are affected with multidrug-resistant tuberculosis (MDR-TB) and are at high risk for morbidity and mortality secondary to COVID-19.
- An outbreak of COVID-19 among the patients screened for or already participating in the trials could disrupt the trials by reason of valuable information being lost; however, more importantly, an outbreak could result in many patients unable to achieve cure (because of treatment disruption or fatal COVID-19).

b. TB and COVID-19

- People ill with COVID-19 and tuberculosis (TB) show similar symptoms such as cough, fever and difficulty breathing.
- The incubation period from exposure to disease in TB is longer, often with a much slower onset.
- While experience on SARS-CoV-2 infection in TB patients remains limited, it is anticipated that people ill with both TB and COVID-19 may have poorer treatment outcomes,[1] especially if TB treatment is interrupted.
- Data collated from over 200 countries has shown significant reductions in TB case notifications between January and June 2020 compared to the same 6-month period in 2019. These reductions in case notifications could lead to a dramatic increase in additional TB deaths, according to WHO modelling.[2]
- This guide advises on how to best manage the endTB trial participants in light of the threat of COVID-19; many of its principles can be applied to all TB programs.

c. How to use this guide

- This document contains practical guidance on how to prevent, diagnose and treat COVID-19 and how to prepare for an efficacious COVID-19 response.
- As a general rule, the national guidelines on how to manage COVID-19 supersede this document.
- How to best manage COVID-19 is a rapidly changing field.
- This document is a living document and will be updated frequently.

- The endTB Study Coordinator will update site Principal Investigators (PIs) and clinicians when new versions are released.
- Epidemiology, disease presentation, transmission information and other useful material can be found in Annex 1.

2. Testing for COVID-19

a. Types of Tests

There are three broad categories of testing used for detecting COVID-19:

1. **Reverse transcriptase polymerase chain reaction (RT-PCR)**
   The PCR test detects the genetic material of the SARS-CoV-2 virus. This type of test is also called a "molecular test." This is considered the gold standard for diagnosing active disease. There are many RT-PCR instruments and platforms approved by stringent regulatory authorities (SRAs).
   Xpert® Xpress SARS-CoV-2- this is an automated molecular test that uses PCR technology and uses the same Xpert® machines as used for diagnosis of TB.

2. **Antigen (Ag) rapid diagnostic test (RDT)**
   This test detects an antigen of the SARS-CoV-2 virus, most often the nucleocapsid protein. Most tests require a nasopharyngeal swab. Sensitivity compared to RT-PCR in samples appears highly variable, but specificity is consistently reported to be high (>97%).

3. **Antibody (IgM/IgG) RDT**
   This test detects antibodies in the blood to SARS-CoV-2. Because this test measures the body's response to the virus there is a window period between infection and having a positive antibody response. There can also be false positives due to cross-reactivity to other coronaviruses that cause the common cold. The antibody test can also stay positive long after the infection has resolved. Given the characteristics of the test, it should NOT be used as the basis to diagnose active COVID-19 rather as a complementary tool to viral testing (RT-PCR or Ag RDT). The antibody test is most commonly used in surveillance and research to determine the percentage of the population that has been exposed to the virus.

Table 2.1 summarizes the different diagnostic laboratory tests for COVID-19 followed by a detailed narrative on each testing category.

Table 2.1. Types of tests

Characteristic	RT-PCR	Antigen (Ag) (RDT)	Antibody (IgM/IgG) RDT
Sample	Nasopharyngeal swab Less commonly a deep sputum specimen is used	Nasopharyngeal swab	Blood (finger stick or blood draw)

Time period for when the test has the best performance (most likely to yield a positive result)	Pre-symptomatic (1-3 days before symptom onset) and early symptomatic phases (first 5-7 days of illness).	Pre-symptomatic (1-3 days before symptom onset) and early symptomatic phases (first 5-7 days of illness).	7-10 days after onset of symptoms
False positives	**Almost none**	**Very Low**	**Low to moderate** It is possible to have cross-reactivity to other coronaviruses different from SARS-CoV-2.
False negatives	**Occasionally** Especially in patients that are a few days after transmission or in patients who present more than 5-7 days after the onset of symptoms.	**Variable** (not as sensitive as RT-PCR)	**Variable** High false negatives when used less than 10 days after the onset of symptoms.
Turn-around time/ Laboratory requirements	Hours - requires a laboratory with high technical capacity.	30 min – No Laboratory required.	15 min – No Laboratory required.

RT-PCR

- RT-PCR is the test of choice for detecting SARS-CoV-2 in the endTB COVID-19 response.
- The most commonly used sample for RT-PCR is the nasopharyngeal swab.
- Testing lower respiratory tract specimens (sputum) for SARS-CoV-2 is an acceptable option in patients who have a productive cough.[3,4] Special processing is needed for thick sputum specimens, using reagents such as dithiothreitol (DTT), to reduce mucoid viscosity.
- Sputum induction techniques should be avoided because of the risk of aerosols exposure.
- The use of saliva is still being studied (see Section C below).
- Under certain clinical circumstances (for example, those receiving invasive mechanical ventilation), a lower respiratory tract aspirate or bronchoalveolar lavage sample should be collected and tested.[5]
- The nasopharyngeal swab can be self-administered[6] by the participant (studies in the USA show that this is less unpleasant to the patient, yields are the same, and there is less chance of exposing the person administrating the swab).
- The RT-PCR test may have a sensitivity of around 75%, which means false negatives can occur. False negatives are more likely a few days after infection, when the virus load is low and below the level of test detection.
- The viral load also drops at about 7 days after the onset of symptoms and RT-PCR testing preforms less well in this time period. It takes longer for the viral load to drop in severe disease.

- There are cases where the RT-PCR remains positive weeks after symptoms have resolved; these patients are not considered contagious and the positivity is likely due to the RNA from dead virus remaining.
- If the RT-PCR is negative but suspicion for COVID-19 remains, then ongoing quarantine and re-testing several days later should be considered (see figure 2.1).
- The Xpert® Xpress SARS-CoV-2 cartridge also uses PCR technology and uses the same Xpert machines as used for TB diagnosis. This test has been granted a WHO Emergency Use Authorization.[7] The cartridges are in short supply and only available through WHO and Global Fund mechanisms in many countries. A class 2 biosafety cabinet is currently recommended for Xpert® Xpress SARS-CoV-2. The use of a simple ventilated work station with full PPE for the technicians is acceptable.

Antigen (Ag) RDTs

Because the RT-PCR tests are expensive and often limited in how many can be done, the Ag RDTs can serve as an easier and less expensive test for widespread testing.

The prevalence of disease determines the positive and negative predictive values (PPV and NPV, respectively) of the RDTs. In a setting with widespread community transmission positive test results have a high PPV. Likewise, the predictive value of a negative RDT result may be low, even when there are strong epidemiologic or clinical indicators of COVID-19 exposure or disease.

Of note, Ag RDTs should meet the WHO guidance on the minimum performance requirements of >80% sensitivity and >97% specificity compared to RT-PCR. The WHO interim guidance on using antigen RDTs was issued in September 2020.[8] As of 15 October 2020, there are two Ag RDTs approved for Emergency Use by the WHO and two positively evaluated by FIND (Table 2.2). We recommend that sites only use Ag RDTs that have received positive evaluation from the WHO or FIND. No Ag RDT should be used before independent evaluation of its performance against the RT-PCR can be done.

Table 2.2 Approved for Emergency Use Ag RDTs

Test Name	Manufacturer	Positively evaluated by
STANDARD Q COVID-19 Ag Test	SD Biosensor Inc.	WHO[11], FIND[9]
NowCheck COVID-19 Ag Test	Bionote, Inc	FIND[10]
Panbio COVID-19 Ag Rapid Test Device (NASOPHARYNGEAL)	Abbott Rapid Diagnostics Jena GmbH	WHO[11]

SARS-CoV-2 Ag-RDTs should not be used when there is low or unknown PPV or NPV (or when the sensitivity and specificity has not been validated from a reliable source) as positive or negative tests would require confirmatory tests for decision making.
In settings with widespread community transmission of the virus, Ag-RDTs can be used in contact cases or individuals presenting COVID-like symptoms to rapidly isolate positive cases and initiate contact tracing and prioritize sample collection from RDT-negative individuals for RT-PCR.

The PPV and NPV may be low in the following situations:

- In individuals without symptoms UNLESS the person is a contact of a confirmed case;
- Where there are only sporadic cases;
- For airport or border screening at points of entry;
- In screening prior to blood donation.

Always follow the specific manufacturer's instructions for performing the test. As more evidence and approvals on the use of Ag RDTs becomes available, this guidance will be updated.

Antibody (Ab) RDTs

- The Ab RDTs are not used to determine active COVID-19 disease. In general the test is used to determine if a person has been previously exposed to COVID-19 and not used for case detection.
- Use of Ab RDTs in populations can help determine the burden of disease and the proportion of a population previously infected with SARS-CoV-2. Thus, demographic and geographic patterns of test results provide data that can be used in forecasts of disease spread that can support resource allocation decisions and planning by local and state officials
- These tests are done on blood (finger stick or blood draw).
- Sensitivity and specificity vary widely depending on the brand of antibody test.[12] Numerous tests are under review by FIND.[13]

Supplemental diagnostic studies include:

- **X-ray or CT-Scan.** Bilateral pneumonia on X-ray or a CT-scan that has ground-glass opacities in the lung parenchyma can also help support the diagnosis of COVID-19.
- **Ultrasound.** Lung ultrasound can also be helpful and shows a characteristic finding of a diffuse B-pattern.

b. Who should be tested?

In endTB trial sites, testing for COVID-19 will be strongly encouraged in the persons and situations described in Table 2.3.

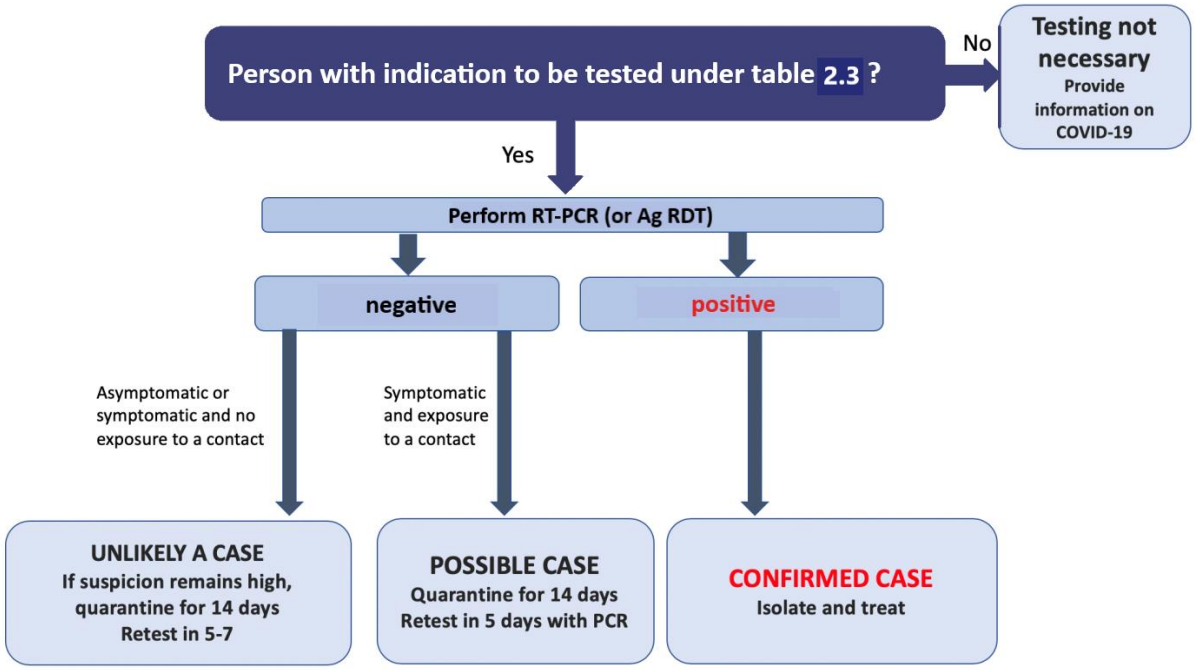
Figure 2.1 illustrates the persons to be tested and the endTB recommended testing algorithm.

Table 2.3 Persons to be tested for COVID-19

Person to be tested	Circumstances
TB patients being screened for entry into the trial.	All, regardless of symptoms
endTB study participants	Known exposure to COVID-19 contact in previous 14 days, regardless of symptoms
	Symptomatic or change in TB symptoms consistent with COVID-19*
TB patients hospitalized alongside endTB study participants (close contacts on the TB wards)	Symptomatic or change in TB symptoms consistent with COVID-19
Health care workers (HCWs) involved in TB facilities associated with endTB	Known exposure to COVID-19 such as exposure without adequate PPE or exposure to a case outside the TB facility in previous 14 days
	Develops symptoms consistent with COVID-19
Household (HH) contacts of endTB Study participants	Presumptive case of COVID-19 in the household
	All HH contacts if there is a known COVID-19 case in the HH

* Study participants should be regularly screened for COVID-19 by a simple questionnaire (see example in Annex 3).

Figure 2.1 endTB testing algorithm for COVID-19



- All HCWs directly involved in TB facilities where the endTB trial activities take place, irrespective of direct contact with the study participants, will be tested under the circumstances of Table 2.3.

- All HH contacts of the study participants will be tested under the circumstances of Table 2.3.

Notes on testing for SARS-CoV-2 in the endTB trial

- The RT-PCR test can be done on the same sputum specimen that was collected as part of endTB screening or follow-up procedures in order to avoid taking multiple samples.
- Participants that are a "possible case" or "confirmed case" of COVID-19 and have no other contraindications to the trial will be allowed entry on a case-by-case basis determined by the site PI and if the participant agrees after being explained the risks/benefits.

Additional thoughts on candidates for testing

- Patients with bilateral pneumonia on chest X-ray are also good candidates to test for COVID-19 as this is a sign highly consistent with COVID-19.
- Chest CT may be helpful in making the diagnosis, but no finding can completely rule in or rule out the possibility of COVID-19. A ground-glass appearance of infiltrates is highly suggestive.
- Data are limited for definitions of close COVID-19 contact. Definition of a close COVID-19 contact a person is defined as follows:
    - Being within approximately 6 feet (2 meters) of a person with COVID-19 for a prolonged period of time (such as sitting within 6 feet of the patient in a healthcare waiting area or room). Data are insufficient to precisely define the duration of time that constitutes a prolonged exposure. However, until more is known about transmission risks, it is reasonable to consider an exposure greater than 15 minutes as a prolonged exposure.
    - Having unprotected direct contact with infectious secretions or excretions of a person with COVID-19 (e.g., being coughed on, touching used tissues with a bare hand).
- Retesting in 5-7 days, where recommended, is to rule out a false negative test (because of testing in window period of RT-PCR).

c. Use of saliva in detection of SARS-CoV-2

Studies are ongoing in evaluating the performances of the use of saliva compared to nasopharyngeal swabs and sputum. There would be many advantages if the testing of saliva could be used, as its collection does not require swabs, trained staff, less PPE is needed, can be done outside of collection centers and is better tolerated in challenging or pediatric populations.

There are several ongoing small studies that examine whether saliva can be used to detect SARS-CoV-2 using various platforms and techniques. However, at present, the WHO[14] and this guide do not endorse the use the universal use of saliva over nasopharyngeal specimens.

Of note, if nasal swabs are not available and the patient is able to produce sputum, sputum can be used with the RT-PCR instruments. If no swabs are available and the patient is not able to produce sputum, saliva is an acceptable option for testing.

d. Viral transport medium

There is currently a global shortage of viral transport medium, the supportive liquid that swabs are transported in after collection.

Without proper transport medium or storage, specimens degrade. This is especially true for the RNA that is detected by an RT-PCR test. RNA is less stable than DNA, so if a specimen is not transported or stored appropriately, the risk of a false negative RT-PCR result increases.

Because specimens can degrade with time, and to be on the safe side, we suggest storing specimens at 2-8°C for up to 72 hours. If transport is not possible within 72 hours, then the sample should be stored at -70°C or below. This is the norm, but most samples will be adequate if they fall outside of this parameter.

A few recent studies demonstrated that collecting a nasopharyngeal swab and placing it in sterile saline (0.9% NaCl) medium is equally effective.[15,16] In one study the samples were stored at 18°C to 25°C, 2°C to 8°C and -10°C to -30°C and then tested at time points up to 14 days. Specimens consistently yielded amplifiable RNA with mean cycling time differences of <3 over the various conditions assayed, thus supporting the use and transport of alternative collection media and specimen types under a variety of temperature storage conditions.

At the time of this writing we only recommend using normal saline as a transport medium when approved viral transport medium is not available.

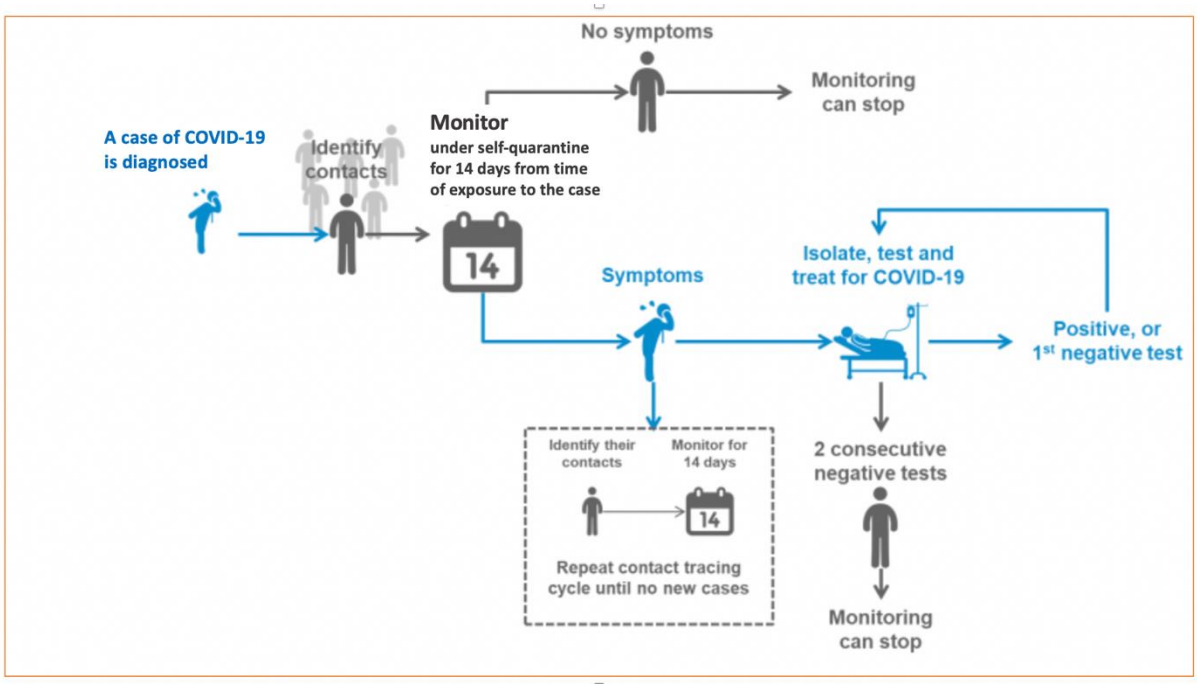
e. Procurement, ordering and forecasting of COVID-19 tests

- Collect information on the national testing strategy and capacity at local level.
- Estimate if endTB will have to order its own tests or if they can readily use the MoH laboratory or other validated testing facilities.
- Estimate testing capacity, ability to get specimens to laboratory, and turn-around time.
- Secure orders of swabs in advance as there is a risk of global shortage of this item.
- Secure orders of Xpert® devices and Xpert® Xpress SARS-CoV-2 cartridge.
- Considering ordering one of the WHO or FIND approved Ag RDTs, especially if RT-PCR testing is of short supply.

3. Contact tracing

- A key strategy to stopping the spread of COVID-19 is contact tracing.
- Figure 3.1 (below) illustrates the flow for contact tracing.
- When any diagnosis of COVID-19 in patient, HCW or household (HH) member is made through the endTB response, the team should inform the MoH and confirm that contact tracing is being done (Figure 3.1); of note, over half the transmission in China was due to household transmission.
- The documented or suspected case of COVID-19 should be separated from the household and be isolated for 14 days.
- If the MoH has insufficient capacity to do contact tracing and testing for cases of COVID-19 in the household of participants, the study team should use endTB resources to do contact tracing.

Figure 3.1. Contact tracing in COVID-19 (from WHO)

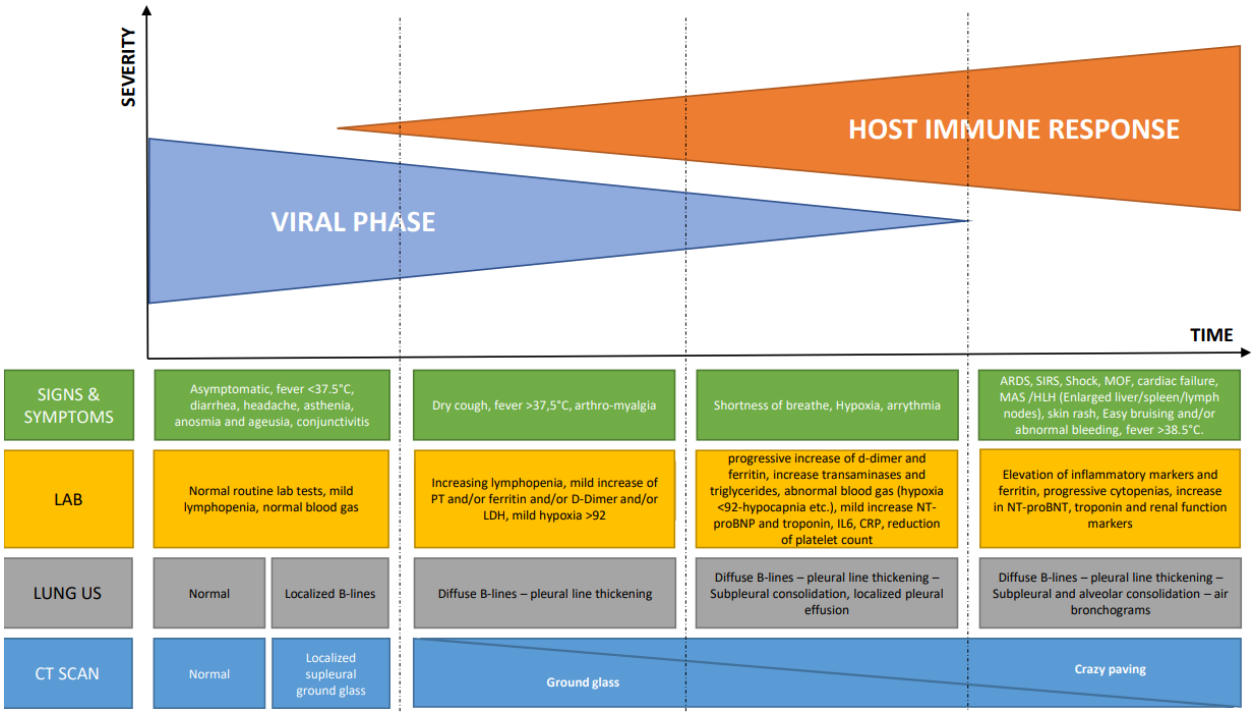


4. Treatment

At the time of this writing there are very few proven therapies for COVID-19. Many drugs are currently under investigation, while several are being employed worldwide in off-label use. Few are available via compassionate use or expanded access mechanisms. **As a general rule, when national guidelines on how to treat COVID-19 exist they supersede this document.**

According to current reports, COVID-19 appears to develop following a biphasic trend (Figure 4.1). During the first phase, patients develop nonspecific signs/symptoms of viral infection, such as fever, weakness, and cough. In the second phase, which usually starts one week after the onset of symptoms, patients develop a hyper-inflammatory response accompanied by signs/symptoms of pneumonia and culminating, in the most severe cases, with the development of ARDS. The treatment options described below here target viral replication with antiviral drugs (e.g., remdesivir) in the first phase, followed by immunomodulatory drugs (e.g., corticosteroids) to control the hyper-inflammatory response in the second phase of the disease.

Figure 4.1. Clinical, instrumental and pathogenetic model of COVID-19. Modified from Galluccio et al.[17]



Antiviral treatment

Table 4.1 shows drugs in current use for COVID-19 that have at least *in vitro* data or minimum *in vivo* data to support their use. At the time of writing this guide there is no clear evidence of their efficacy in humans. All the drugs proposed below are off-label for the treatment of COVID-19. Therefore, patients should be extensively counseled regarding the risks and benefits of their use. **Oral or written informed consent should be obtained prior**

to using any COVID-19 drugs as required by the country or site for off-label use of drugs. Treatment options will be revisited as new evidence emerges. Research should be encouraged. When possible, patients treated for COVID-19 should be proposed to enter observational studies or other approved clinical research studies.

Table 4.1. COVID-19 antiviral treatment options for consideration by clinicians

Drugs (formulation)	Available evidence and posology
Remdesivir (100 mg vials)	On 01 May 2020, the U.S. FDA issued an Emergency Use Authorization[18] for remdesivir based on the preliminary results of the ACTT-1 trial, now published, which showed that remdesivir, when compared with placebo, shortened the time to recovery in adults hospitalized with COVID-19 and evidence of lower respiratory tract infection.[19] The benefit observed in ACTT-1 was reported as most apparent in participants with moderate disease; however, the study follow-up may have been insufficient to detect improvement in a portion of patients with severe disease. In contrast, results from a subsequent open-label randomized controlled clinical trial performed in patients[20] who did not require oxygen showed only a modest clinical benefit for a 5-day remdesivir course compared to the control arm, and no benefit for a 10-day remdesivir course. Other available evidence for remdesivir includes: a) an uncontrolled trial showing overall good safety results,[21] b) a randomized controlled trial which was stopped early for insufficient recruitment and did not show superiority of remdesivir towards placebo,[22] and c) a randomized trial comparing patients receiving 5 and 10 days of remdesivir which showed similar outcomes in the two groups, although results suggest that patients who progress to mechanical ventilation may benefit from 10 days of remdesivir treatment.[23] After evaluating the available evidence with the GRADE methodology, a WHO Guideline Development Group recently concluded that **remdesivir is not suggested** for hospitalized patients with COVID-19, regardless of how severely ill they are, because there is currently no evidence that it improves outcomes that matter to patients such as reduced mortality, need for mechanical ventilation, time to clinical improvement and others.[24] Posology: 2 vials IV once (day 1 loading dose), followed by 1 vial IV daily for 4 or 9 days.
Hydroxychloroquine (200 mg) Chloroquine (100 mg)	Initial studies supporting the use of hydroxychloroquine were observational and conducted on limited number of participants.[32] Promising preliminary findings have not been confirmed by recent reports, including two recently-published large retrospective studies.[25,26,27,28] In addition, two large randomized controlled trials have recently discontinued the investigational arm containing hydroxychloroquine because of lack of efficacy based on an interim analysis.[29] In light of these findings suggesting a lack of efficacy of hydroxychloroquine, and the attendant risks of toxicity and drug-drug interactions with its use, the use of hydroxychloroquine is discouraged.

Boosted protease inhibitors (lopinavir/ritonavir (200/50 mg), darunavir (800 mg) plus ritonavir (100 mg), darunavir/cobicistat (800/150 mg))	Of note, little evidence is available on the efficacy of protease inhibitors to treat COVID-19. A randomized controlled trial has shown that lopinavir/ritonavir was not superior to standard of care in severe COVID-19 cases.[30] Recently, a large multinational randomized controlled trial has discontinued the investigational arm containing lopinavir/ritonavir because of lack of efficacy based on an interim analysis. In light of these findings suggesting a lack of efficacy of lopinavir/ritonavir, and the attendant risks of toxicity and drug-drug interactions with its use, the use of boosted protease inhibitors is discouraged.
Favipiravir (200 mg)	Of note, the evidence on the efficacy of favipiravir to treat COVID-19 is inconclusive and mainly based on an unpublished study.[31] Posology: 8 capsules twice daily for 1 day, followed by 3 capsules twice daily for 13 days.
Azithromycin (500 mg)	Of note, evidence on the efficacy of azithromycin to treat COVID-19 is anecdotal and based only on a small case series,[32] which has not been confirmed in a large retrospective study. [28] Posology: 1 capsule daily. Total treatment duration is between 5 days and three weeks (as for hydroxychloroquine).

Immunomodulatory treatment

Table 4.2 shows drugs in current use for COVID-19 that have minimum *in vivo* data to support their use. To date, corticosteroids are the only medical intervention with the potential to improve survival in (a subgroup of) patients with COVID-19.

Table 4.2. Immune system modulators which may be considered for COVID-19 treatment

Drugs	Available evidence and posology
Corticosteroids	Studies have shown no benefit associated with the use of corticosteroids in the treatment of disease caused by SARS-CoV-1 and MERS-CoV.[33,34] However, a randomized controlled clinical trial found that dexamethasone could reduce mortality among patients with moderate-to-severe ARDS.[35] Recently, a large randomized controlled clinical trial (RECOVERY) showed a mortality reduction in patients hospitalized with COVID-19 treated with dexamethasone, when compared to usual care.

	This benefit appeared to be restricted to patients receiving oxygen or invasive mechanical ventilation.[36] A recent meta-analysis of seven randomized clinical trials, including RECOVERY, evaluating treatment with corticosteroids (dexamethasone, hydrocortisone, and methylprednisolone) confirmed these findings.[37] Posology: The following treatment scheme may be employed: Dexamethasone IV 6 mg daily for up to 10 days. In alternative, the use of hydrocortisone or methylprednisolone may also be considered. A simple web-based corticosteroid conversion calculator can be found here: https://www.mdcalc.com/steroid-conversion-calculator
Tocilizumab	Tocilizumab is a human interleukin-6 receptor antibody. Its use could be considered in severe COVID-19 cases (with or without ARDS) with signs of hyper-inflammatory syndrome (i.e., increased C-reactive protein, D-dimer, IL-6), and in any case only after the viral response phase is over (i.e., starting from day 8 since the beginning of COVID-19 signs/symptoms). A company-sponsored randomized clinical trial was recently reported to have failed to show a mortality benefit in COVID-19 patients treated with tocilizumab, when compared to placebo.[38] However, the small sample size of the study should be noted. Tocilizumab is being studied through a second randomization in COVID-19 patients with hypoxia and signs of inflammation in the RECOVERY trial: results will hopefully provide further insight on the efficacy and safety of this drug. Tocilizumab can alter the immune system response for many months after the administration. Major contraindications include ongoing sepsis or acute diverticulitis. All patients should be screened for active hepatitis B virus infection, and treated if positive, prior to administration. In addition, patients who are not affected by active tuberculosis should be screened for latent tuberculosis infection (LTBI) before initiating treatment, and, if tested positive, they should receive LTBI treatment after the COVID-19 episode is resolved. Expert advice should be sought to design the LTBI treatment regimen. This is particularly true for patients who are household contacts of patients with active tuberculosis who receive tocilizumab. **Patients with active tuberculosis should not receive tocilizumab except in selected, severe cases with no treatment alternatives.** Posology: 8 mg/kg per administration (maximum 800), as follows: one IV infusion, followed by a second one after 8-12 hours, and an optional one after 16-24 hours from the first one.

Supportive treatment

- Antibiotic treatment: in patients being ruled out for or who have confirmed COVID-19, who are receiving care from a facility that is not prescribing azithromycin

systematically for COVID-19, clinicians should consider azithromycin as the drug of choice when they cannot exclude community acquired pneumonia. Clinicians should assess the need for azithromycin with concomitant ceftriaxone based on the severity of presentation. For hospitalized patients, the combination of ceftriaxone and azithromycin is preferable. Antibiotic treatment should be adapted to local epidemiology and prevalence of bacterial resistance.

- Other supportive treatment: in hospitalized/bedridden patients with no specific contraindications or risk factors for bleeding, low molecular weight heparin (i.e. enoxaparin) is indicated, at a prophylactic dosage (i.e., 4000-6000 UI once/day according to body weight). The use of low molecular weight heparin at therapeutic anticoagulation posology has been contemplated for the treatment of selected COVID-19 patients, including critically-ill patients with high levels of D-dimer, increased inflammatory markers, and/or multiorgan failure. Observational evidence supports the use of low molecular weight heparin in COVID-19 patients, but not the benefit of administering it at therapeutic posology.[39]

Who to treat

Given the absence of clear evidence on the efficacy of antiviral drugs, and the lack of well-established international recommendations on their use, the choice to treat should be based in every case on an individual evaluation of the risk/benefit ratio, depending on drug availability and on risk of additive toxicity/interaction with other treatments the patient is taking. If possible, participation to clinical research should be encouraged. If participation to clinical research is not possible, the following elements could be considered:

- Patient with severe COVID-19 pneumonia[40] with/without acute respiratory distress syndrome are most likely to benefit from treatment, except for specific individual contraindications.
- Patients with symptomatic, confirmed COVID-19[41] and need for oxygen support treatment are likely to benefit from treatment in most cases, at least with an immunomodulatory agent;
- Among patients with symptomatic, confirmed COVID-19[42] who do not need oxygen support, those with risk factors for unfavorable outcome* are more likely to benefit from treatment (i.e., with an antiviral agent);

There is currently no evidence regarding treatment of asymptomatic patients with confirmed COVID-19; in this group, even among patients with risk factors for unfavorable outcome, treatment is unlikely to be beneficial. Similarly, there is at present no evidence to support a “prophylactic” treatment of patients exposed to COVID-19 cases.

**Risk factors for unfavorable outcome* include: age >65 years, immunocompromising conditions, active malignancy, structural lung disease, chronic kidney disease, hypertension, coronary artery or other cardiac disease, diabetes, or BMI >30. All active TB patients should be considered to be ‘high-risk’ for COVID-19 complications. Structural lung disease is generally underdiagnosed in this population, notwithstanding other comorbidities. A possible exception might be represented by patients with very mild disease or largely improved from their tuberculosis.

Treatment monitoring

Home-based or ambulatory-based patients receiving COVID-19 drugs which have the potential to prolong the QT interval (azithromycin, hydroxychloroquine/chloroquine, and, to a lesser extent, boosted protease inhibitors) should perform a baseline ECG if any of the following risk factor is present:

- treatment with other QT-prolonging drugs;
- hypokalemia, hypomagnesaemia, or hypocalcemia;
- bradycardia;
- underlying cardiac disease, including long QT syndrome;
- age >70 years.

In case of prolonged corrected QT interval, blood tests should be performed to check blood potassium, magnesium, and calcium. In addition, if the prolonged corrected QT interval lies between 450 and 500 ms, close ECG monitoring should be performed; if the corrected QT interval is equal or higher than 500 ms, these drugs should not be administered.

Hospitalized patients receiving azithromycin, hydroxychloroquine/chloroquine, or boosted protease inhibitors, should perform an ECG every day, if possible.

Special considerations for TB patients

Treatment of COVID-19 poses additional challenges in patients with active TB. Table 4.2 summarizes the main elements to be taken to account in the concomitant treatment of these two diseases.

Table 4.2. Special considerations for COVID-19 treatment in TB patients

	Advice
Drug-drug interactions and concomitant treatment for TB and COVID-19	Special attention should be paid to the following possible drug-drug interactions between COVID-19 and TB drugs: • Rifampicin substantially decreases the blood concentrations of boosted protease inhibitors, and moderately decreases blood concentrations of hydroxychloroquine/chloroquine and remdesivir. Rifabutin may have less substantial interactions. • Boosted protease inhibitors increase blood concentrations of bedaquiline and delamanid. For patients receiving TB treatment and in need of COVID-19 treatment, the risk/benefit of concomitant treatment should be assessed: possible options are not treating for COVID-19, adapting TB/COVID-19 treatment to avoid interactions (and additive toxicities), or withholding TB treatment for a few days. The latter option may the preferred one for patients with severe COVID-19 (or with ARDS). In addition, lopinavir/ritonavir, darunavir, ritonavir, and darunavir/cobicistat are disallowed for trial participants receiving bedaquiline as per endTB and endTB-Q study protocols. If treatment with these drugs is considered in such a

	circumstance, it is advised to discuss it on a case-by-case basis with the Clinical Advisory Committee. A useful reference for drug-drug interactions of drugs for COVID-19 is the following: http://www.covid19-druginteractions.org
QT interval prolongation	The risk of QT interval prolongation is increased by the use of some second-line anti-TB drugs (moxifloxacin, bedaquiline, clofazimine, delamanid, levofloxacin) and some drugs used for COVID-19 (azithromycin, hydroxychloroquine/chloroquine, boosted protease inhibitors). The use of QT-prolonging COVID-19 drugs should be avoided, if possible, in patients who are already receiving QT-prolonging TB drugs. If multiple QT-prolonging drugs have to be associated, the frequency of ECG monitoring (described above) should be increased to prevent potentially life-threatening arrhythmias.
Tocilizumab use	Because of the long-term risk of immune depression, the use of tocilizumab or other biologics should be avoided in patients with active TB. Possible exceptions may be represented by selected patients with ARDS and no treatment alternatives.

Oxygen therapy

Oxygen therapy relieves hypoxemia and prevents the complications associated with chronic tissue hypoxia. In cases of severe COVID-19 pneumonia, hypoxemia can develop abruptly and should be treated expeditiously. In order to assess and monitor the degree of hypoxemia, both pulse oximetry and arterial gas analysis should be available at the site. In order to deliver oxygen therapy, the following devices should be available at a minimum:

- Low-flow delivery systems like nasal cannula (up to 6 liters/minute);
- Mask with reservoir (8-15 liters/minute).

In addition, sites should consider acquiring the following devices:

- High-flow delivery systems like high-flow nasal cannula;
- Non-invasive ventilation devices like helmets for the delivery of continuous positive airway pressure (CPAP).

Given that these devices aerosolize patient secretions, they should be used for patients in isolation in a negative pressure room with proper personal protective equipment for healthcare workers**.**

5. Infection Control

Overall, the most effective preventive measures include: maintaining physical distance (a minimum of 2 m) from other individuals; performing hand hygiene frequently; avoiding touching eyes, nose, and mouth; respiratory hygiene by coughing or sneezing into a bent elbow or tissue; wearing of appropriate personal protective equipment for healthcare workers; a surgical mask for TB patients, members of their household and people with respiratory symptoms; routine cleaning and disinfection of frequently touched surfaces.[43]

In health care activities, the main infection prevention and control (IPC) strategies to prevent or limit COVID-19 transmission include the following:

Standard infection control precautions

Standard precautions are meant to reduce the risk of transmission of bloodborne and other pathogens from both recognized and unrecognized sources. They are the basic level of infection control precautions which are to be used, as a minimum, in the care of all patients (e.g., hand hygiene, sharps safety, safe injection practices, etc.). These practices are designed to both protect HCW and prevent HCW from spreading infections among patients.[44]

Staff pre-screening

Implement a daily pre-screening questionnaire to all trial site staff (clinical, laboratory, administrative, etc.) before staff can start work for the day.

An example questionnaire is presented in Annex 3. It includes the following questions that may be adapted to local pre-screening tools:

Are you experiencing any of the following symptoms? [1] fever or feeling feverish, [2] sore throat, [3] new cough, [4] new nasal congestion or new runny nose, [5] muscle aches, [6] new loss of smell, [7] shortness of breath.

If a staff reports none of the above symptoms, then they are cleared to work. However, if positive for any of the symptoms at pre-screening, then the staff shall NOT be cleared to work for the day and should be referred for testing by RT-PCR or AG RDT.

Discontinuing isolation and returning to work (adapted from CDC[45])

People with mild to moderate COVID-19 remain infectious no longer than 10 days after their symptoms began, and those with more severe illness or those who are severely immunocompromised remain infectious no longer than 20 days after their symptoms began. Therefore the recommendations for discontinuing home isolation as follows:

Persons with COVID-19 who have symptoms and were directed to care for themselves at home (mild or moderate illness) may discontinue isolation when all three of the following conditions exist:

- At least 10 days* after symptom onset **and**
- At least 24 hours after resolution of fever without the use of fever-reducing medications **and**
- Other symptoms have improved.

*** A limited number of persons with severe illness** may produce replication-competent virus beyond 10 days, that may warrant extending duration of isolation for up to 20 days after symptom onset. When symptoms are not improving, the duration of isolation can be determined on a case-by-case basis and could exceed 20 days after onset of symptoms.

Asymptomatic persons with COVID-19 may discontinue isolation 10 days after their first positive test that detects the virus (Ag RDT or RT-PCR tests).

Persons infected with SARS-CoV-2 who never develop COVID-19 symptoms may discontinue isolation and other precautions 10 days after the date of their first positive RT-PCR test for SARS-CoV-2 RNA.

Role of testing for discontinuing isolation or precautions:
RT-PCR testing for detection of SARS-CoV-2 RNA for discontinuing isolation could be considered for persons who are severely immunocompromised.[45]

For all others, a test-based strategy for discontinuing isolation is no longer recommended.

The test-based strategy requires negative results of RT-PCR from at least two consecutive respiratory specimens collected ≥24 hours apart (total of two negative specimens).

Triage for all patients, caregivers or visitors accessing endTB sites

We recommend a preliminary screening point, ideally at the entrance of the medical facility (e.g. at the main gate). The purpose of this screening and its importance should be explained to those visiting the facility (i.e. why individuals are being screened for COVID-19). There should be dissemination of accurate information on infection prevention and control (such as hand hygiene, respiratory and cough hygiene etc.). Public service announcements could be made in print or media.

Preliminary screening includes the use of no-touch thermometers, limited observation and relevant questioning (e.g., complaints of fever/cough/difficulty breathing , travel history or contact with someone infected with COVID-19 or appropriate case definition used in respective settings), while maintaining a spatial distance of at least 2 m (6 feet). Floor marking can help materializing the spatial distance.

All patients, people visiting the facility and healthcare workers should have access to and wear appropriate PPE when entering the facility (see Table 5.1). Triage and waiting areas should be properly ventilated with appropriate infection control measures in place especially in closed environments. Ensure spatial separation (of at least 2 m) between patients in the waiting area or in queues for any examinations. This can also be implemented by reviewing clinic schedules to limit inflow of scheduled patients at the same time. If possible, create separated waiting area and consultation room for suspected COVID-19 patients identified at the preliminary screening.

Personal Protective Equipment (PPE)[46,47]

All health care workers, cleaners, caregivers, visitors etc. should wear specific PPE that may be adapted according to their activity area (triage, consultation, drug delivery, nasopharyngeal sampling, cleaning, while operating with a suspected or confirmed case of COVID-19 infection (refer to table 5.1).

Table 5.1. Recommended PPE per area, person and activity in settings with community transmission (To be adapted to each setting)

Area	Target people	Activity	Surgical mask	Respirator FFP2 or N95	Surgical gown	Disposable or reusable gown	Disposable gloves	Heavy duty gloves	Eye protection	Boots or closed work shoes		Apron
Triage	Healthcare workers	Preliminary screening not involving direct contact (maintain distance)		X								
	Patients with symptoms	Move the patient to an isolation room or separate well ventilated area	X									
Consultation rooms	Healthcare workers	Physical examination of patient with respiratory symptoms		X		X	X		X			
	Patients	Any	X									
	Cleaners	After and between consultations with patients with respiratory		X		X		X		X		

		symptoms.										
Home visits	Healthcare workers	Care requiring close contact[a] (clinical examination, etc.)		X		X	X		X			
		No close contact (DOT supervision from distance, contact investigation by in-person interview)		X								
	Patients	Any	X									
Inpatient rooms	Healthcare workers	Providing direct care and in close contact		X		X	X					
	Patients	Any	X									
	Cleaners	Cleaning the area		X		X		X		X		
	Care takers or visitors	Any		X		X	X					
COVID Isolation area	Healthcare workers	Providing direct care and in close contact (aerosol generating procedure)		X	X	X	X		X			X[b]
	Patients	Any	X									
	Cleaners	Cleaning the area		X		X	X		X	X		
	Healthcare takers	Entering the isolation area		X		X	X		X			
Offices, pharmacy, and other “clean areas”.	Any	Any	X[c]									
		Handling drugs returns	X		X		X					
Remote contacts (e.g., by phone or videoconference)	Healthcare workers	Contact investigation, Video DOT, patient information and follow-up	No PPE									
	Patients	Any										

[a] Close contact defined as being within approximately 2 meters for a prolonged period of time or having direct contact with infectious secretions of a of a probable or confirmed COVID-19 case (e.g., being coughed on)[48]
[b] When performing aerosol generating procedures (e.g. tracheal intubation, non-invasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation, bronchoscopy)[c] When social distancing is not possible (see below).

A poster showing how to put and remove PPE is presented in Annex 4. Gloves will have to be disposed between each patient, suspected or confirmed.

For any aerosol generating procedures, recommend access to negative pressure rooms. Nasopharyngeal swab sampling should be performed in a designated area by trained personnel.

Minimizing the need for PPE in health care settings[49,50]

There is a global shortage of PPE and it is therefore essential to rationalize its use. The need of PPE can be minimized by adapted organization of care and extended use or reuse.

Minimize number of people who need PPE

- Restrict the number of HCW in contact with patients if they are not involved in providing direct care.
- Designate a subset of HCW who must interact directly with the patient. This will also allow them to use PPE for longer periods of time (extended use of PPE), if necessary.
- The above measures also limit the risk of exposure for the HCW.
- Use specific PPE only if in direct close contact with the patient or when touching the environment (e.g., not using gloves or gown, if entering the patient's room only to ask questions or make visual checks).

Concentrate care delivery

- Streamline the workflow and reduce to a safe level care that requires face-to-face interaction between health worker and patient. Develop strategies to complete multiple tasks utilizing the same set of PPE. For example: taking vital signs and giving medication at the same time.

Extend use of PPE

Extended use is preferred over reuse because there is less risk of spreading the virus.

- *Gowns:*

Disposable gowns may be worn continuously as a provider moves between patients in a ward.

- *Respirators:*

Extended use of respirators between patients can be considered without removing up to 6h, (meaning that the respirator is not removed between patients but stays on a provider's face continuously). The prolonged period may increase the chance of health care workers touching the respirator or having inadvertent under-respirator touches; if respirator masks are touched/adjusted, hand hygiene must be performed immediately.

Reuse PPE

The removal, storage, re-donning, and reuse of the same, potentially contaminated PPE items without adequate reprocessing is one of the principal sources of risk to health care workers.

- *Face Shields and Goggles:*

Clean with soap/detergent and water and disinfection with 70% alcohol or sodium hypochlorite 0.1%. Appropriate contact time with disinfectant (e.g. 10 minutes when using

sodium hypochlorite 0.1%) should be adhered to. Finally rinse with clean water if sodium hypochlorite is used. Ensure cleaning takes place on surface without contamination. Disinfection of surface for cleaning is advised.

- *Gowns:*

If disposable gowns are in short supply, reusable gowns can be considered with adequate laundering (see section on cleaning).

- *Respirators:*

Extended use is preferred. Respirators may be reused during a single shift (meaning removed from the face and then put back on in between patients) at the following conditions:50[50]

- Respirators must be worn by a single wearer;
- Respirators must be put and removed following instructions (see Annex 4);
- The removed respirator should be placed in a designated receptacle for reuse (not worn on the forefront or under the chin);
- Avoid touching the inside of the respirator. If inadvertent contact is made with the inside of the respirator, discard the respirator and perform hand hygiene.
- Perform hand hygiene immediately before and after putting on or otherwise touching a reused respirator;
- Respirators must be replaced when dirty or damaged or used during an aerosol generating procedure.
- Preliminary data[51,52] suggest limiting the number of reuses to no more than five uses per device to ensure an adequate safety margin.

Reprocessing methods of respirator masks have not been validated and there are currently no standardized methods or protocols for ensuring the effectiveness of the respirators after reprocessing.

Cleaning

Contaminated gowns and textiles should be handled with a minimum of agitation in order to prevent the generation of contaminated aerosols. Contaminated textiles should be placed into bags that are then securely tied to prevent leakage. Bags containing contaminated laundry must be clearly identified with labels. Gowns should be either washed within the hospital or at an industrial laundry that meet antimicrobial standards. Washing at home should be avoided.

All waste should be considered as infected in this environment. PPE should be discarded in an appropriate waste container after use, and hand hygiene should be performed before putting on and after taking off PPE.

All surfaces including equipment used during for examinations or consultations need to be cleaned with appropriate disinfectants (e.g., 0.1% sodium hypochlorite or bleach solution) in between patient visits. Additional staff may be required to maintain facility hygiene with appropriate staff rotations. More frequent cleaning and disinfection may be required based

on level of use. High touch surfaces include: tables, doorknobs, light switches, countertops, handles, desks, phones, keyboards, toilets, faucets, sinks, etc.

Contact minimization

Consider the use of physical barriers to reduce exposure, such as glass or plastic windows in areas of the health care setting where patients will first present, such as triage and screening areas, the registration desk at the emergency department, or at the pharmacy window where medication is collected.

When no direct contact with the patient is needed, use telephone (contact tracing, clinical evaluation, patient follow-up, remote DOT, patient information, etc.) thus minimizing the need for these persons to go to health care facilities and staff exposure.

Pharmacy, offices and other clean areas (Adapted from WHO[53])

Measures to prevent transmission of COVID-19 that apply to all workplaces and all people at the workplace include frequent hand-washing or disinfection with alcohol based hand sanitizer, respiratory hygiene, physical distancing of at least 1.5 meters, wearing of masks where distancing is not possible, and regular environmental cleaning and disinfection.

Sufficient space, of at least 10 square meters is required for every worker. This may require modification of workstations, changing the use of common spaces and transport vehicles, staggered work shifts, etc. National recommendations for physical distancing may require greater physical distance and should be complied with.

Stimulate workers to comply with physical distancing norms also at events outside the workplace and in the community.

If physical distancing measures at the workplace are not feasible for specific work tasks, consider whether the work can be done from home, and if this is not possible, apply additional protective measures, such as the use of screens, sneeze guards, face masks in addition to enhanced hand hygiene, ventilation and disinfection.

Handling of drugs returns

Guiding principles:

- All the returns should be considered potentially infected including IPs, DOT cards, blister packs, pill boxes, etc.
- Coherence between actual patient returns and DOT cards should be checked by study staff wearing adequate PPE to allow for initial IP accountability and adherence recording;
- Handling returned IP and material with proper PPE in dedicated ventilated area
- If possible, decontamination of all returns through quarantine (28 days) in a dedicated place outside the pharmacy will allow:
    - Final returned IP- DOT card check/monitoring before destruction of Ips according to local requirements;

  - Re-use of re-usable pill planners after disinfection;
  - Blister packs to be disposed as hazardous waste (either immediately after un-blistering of any extra IP dose or after quarantine).

- If not possible, IP and containers are disposed immediately at hospital as hazardous waste. If reusable containers can be reused after disinfection.

Visitors

All non-employees should be considered visitors. Therefore, number of visitors should be restricted. This can be done by allowing only one person to accompany a patient. If visitors must enter a COVID-19 patient's room, they should be provided with clear instructions about how to put on and remove PPE and about performing hand hygiene before putting on and after removing PPE; this should be supervised by a healthcare worker.

In order to reduce PPE consumption, a separate visitor area could be set-up, ensuring a spatial distance of at least 2 m between the patients and the visitors.

Patient flow

Patient transport within the facility should follow PPE guidelines for COVID-19 patients at that facility. Avoid movement of suspected or confirmed COVID-19 patients. If it is necessary (for example to reach the X-ray room), suspected or confirmed patients should wear a mask. Make sure there is a preparedness plan for ambulance or assisted transfers. Transfer staff should wear appropriate PPE based on COVID-19 infection in catchment area.

Administrative measures

Consider maintaining a register of visitors and their contact information. This may later aid in contact tracing. Designate a preparedness committee for COVID-19 with a clearly identified lead on infection prevention and control. This could be repurposed from existing emergency management committees at the facility. Designate a staff lead for training of all employees regarding COVID-19 (to cover updates, latest recommendations etc.).

Quarantine and Isolation

Quarantine of persons is the restriction of activities or separation of persons who are not ill, but who may have been exposed to an infectious agent or disease, with the objective of monitoring symptoms and early detection of cases. Isolation is the separation of ill or infected persons from others, so as to prevent the spread of infection or contamination.
Post-exposure quarantine is usually of 14 days.
The time period of isolation depends on the patient's severity of illness and if they are severely immunocompromised (also see paragraph "Discontinuing isolation"):

- Usually 10 days from the onset of symptoms for patients with mild or moderate illness;
- Up to 20 days for severe illness or severe immune-depression.

Practical infection control guidance around data collection

In order to not expose data collection staff, data collection practices must adapt. For example, paper forms should not exit isolation areas and data collection staff should not enter these areas unless they are equipped with appropriate PPE and there are no other options for extracting the data.

In order to continue collecting data under these circumstances, we recommend that clinicians with appropriate PPE use paper forms to record vital information.

Cell phones or tablets that are brought out of the isolation unit must be sterilized with alcohol (advised only for water-resistant or waterproof cell phones and tablets).

If physical access to the office is restricted, remote data entry and monitoring is possible if basic data security measures are in place (refer to the document "Privacy recommendations for endTB sites staff in COVID-19 pandemic" (May 2020).

6. Patient Support and Education

Consider providing financial, infection prevention and food support to limit risk of exposure to COVID-19 infection to TB patients and their households. The need for such support may vary across settings and is dependent on local context and resources provided by the program or government. Recommendations that can be adapted to local context are reported below.

Support for infection prevention and control

- **Household assistance package:** Consider offering to all households (identified through endTB as being affected by COVID-19) packages containing: food, household necessities, supplies for infection control such as hand sanitizers, cleaning supplies, masks, gloves, plastic curtain for partition etc.

- **Hospitalization and Isolation:** In several countries existing TB isolation facilities are being repurposed to isolate patients infected with COVID-19. This can create infection prevention control issues for TB patients (including those co-infected with COVID-19) as well as cause disruption in TB services at the facility. In addition, in many low-income countries, where TB patients reside in poor, crowded spaces, it may be impossible to quarantine or isolate patients or their household contacts at home if exposed to COVID-19 infection. Therefore, we recommend that sites should adapt to local context and develop contingency plans that will require creative solutions to finance options that suit local policy and cultural context. These could include identifying properties with independent rooms for quarantine or isolation. In addition, both public and private hospitals should be assessed for infection control set up to ensure access to adequate isolation and in-patient care services for MDR-TB patients (who may or may not be co-infected with COVID-19).

Food assistance

TB patients and their families are most vulnerable to any disaster such as the COVID-19 pandemic. As local activities and economies get affected during this crisis, TB patients will likely suffer the most due to price hikes in food items and basic utilities. This applies to not just TB patients but members from within their family who may be breadwinners and are also at risk for COVID-19 infection. Thus, it is important to enhance food/social assistance packages for affected families that include essential items that are adapted to local context.

Patient education and mental health counseling

We recommend patient education materials be made easily available – in print or media – to TB patients and their families. In addition, consider additional measures to address and prevent mental health issues during long periods of isolation. This could be done through phone calls (audio or video) or text messages or access to call centers etc.

7. Human Resource Planning

In a time of any crisis, particularly one relating to infectious disease such as Covid-19, contingency plans for delivering essential healthcare services must be developed. In developing these, the following assumptions apply:

1. All efforts are made for all appropriate preventive measures to protect the healthcare workforce from falling sick.

2. All efforts are made to maintain the healthcare workforce through rescheduling. For example, for essential health workers consider altering or canceling vacation/leave (except for essential medical leave).

3. By necessity, when qualified health workers fall ill and the tasks to be performed are essential, other health workers may need to be cross trained to fill the role. Every effort will be made to maintain quality of services and patient safety. It is possible that extreme circumstances may require creative thinking and adaptations to deploy healthcare workers either from other areas or through temporary recruitment in order to rapidly learn the essential skill set for their temporary new role.

With the above in mind, the mainstay of human shortages relies on three types of responses:

1. Ensure current services are staffed up with a view to prevent potential shortages in the future. Therefore, based on existing human resource and patient burden, sites should plan ahead and hire additional critical staff at facilities such as doctor, nurse, community health worker etc. These may be able to replace and step in for a defined period of time to prevent any gaps in patient care.

2. With any crisis such as with Covid-19, it is likely that many health workers across the institution will be temporarily asked to work from home. This group represents a pool of workers to cross-train for essential work roles in the clinic or hospital.

3. Consider remote methods such as telehealth for non-essential patient consultations (e.g. during lockdowns or curfews) such as follow-up, routine clinical advice, directly observed therapy, counseling etc.

Annex 1. Epidemiology, disease presentation, transmission, and prevention strategies

a. Epidemiology and disease presentation

- Most people with COVID-19 develop only mild or uncomplicated illness with flu-like symptoms of muscle pain, fever and mild respiratory symptoms. Depending on the testing policy in the country many of these people may never be diagnosed for SARS-CoV-2.
- Little is known about how TB will interact with COVID-19. It is likely that patients with TB-related lung damage will increase risk of severe COVID-19 disease.
- Median incubation period: approximately 5 days.
- Symptoms usually appear within approximately 12 to 14 days of infection.
- Clinical syndrome is non-specific, characterized by:
    - Fever at any time during the illness, 88-99%
    - Cough, 59-79%
    - Dyspnea, 19-55%
    - Fatigue, 23-70%
    - Sputum production, 23-34%
    - Myalgia, 15%-44%
    - Sore throat, 14%
    - Headache, 6-14%
    - Nausea or vomiting, 4-10%
    - Diarrhea, 3-10%
    - Loss of taste and smell (percentage unknown)
- Approximately 80% of laboratory-confirmed patients have had mild to moderate disease, 15% have had severe disease (requiring oxygen), and 5% have been critically ill (requiring intensive care with mechanical ventilation). These percentages are provisional as they are derived from non-representative testing (i.e., disproportionately testing those symptoms and risk factors).
- The most severe cases are characterized by acute respiratory distress syndrome (ARDS), in which the lungs become stiff and oxygenation only can be maintained by mechanical ventilation.
- Other severe complications of COVID-19 include septic shock and multi-organ failure.
- Older people and those with comorbidities (such as diabetes, asthma, and cardiovascular disease) appear to be at significantly higher risk of severe disease.
- The course of COVID-19 is not well known in patients with TB, HIV, viral hepatitis, malaria or malnutrition.

b. Mechanism of transmission

The virus is thought to spread mainly from person-to-person between people who are in close contact with one another (within about 2 meters):

- Spread by contact with respiratory droplets of one individual onto mucous membranes of another individual, such as when coughing or sneezing; aerosol transmission has not been ruled out.
- These droplets can land in the mouths or noses of people who are nearby or possibly be inhaled into the lungs.

The virus can also be spread from contact with contaminated surfaces or objects:

- It may be possible that a person can get COVID-19 by touching a contaminated surface or object that has the virus on it and then touching their own mouth, nose, or possibly their eyes.
- The period of time the SARS-CoV-2 virus can survive in the air and on surfaces depends on the type of surface (metal, wood, plastic, etc.) and other environmental conditions, but can be between minutes to days.

How easily does this virus spread?

- People are thought to be most contagious near the onset of illness.
- The SARS-CoV-2 can spread before people show symptoms of COVID-19.
- COVID-19 seems to be spreading easily and sustainably in the community.

c. General primary prevention

Our main priority for the endTB trial participants is to prevent them from being infected by the SARS-CoV-2 and getting COVID-19 in the first place. endTB trial participants should be fully informed on how they can protect themselves from being infected by the SARS-CoV-2.

The only way to prevent infection is to avoid exposure to the virus in the following ways:

- Wash hands often with soap and water or an alcohol-based hand sanitizer and avoid touching your eyes, nose, and mouth with unwashed hands.
- Avoid close contact with people (i.e., maintain a distance of at least 2 meters), particularly those who have a fever or are coughing or sneezing.
- Practice good respiratory hygiene (i.e., cover mouth and nose with tissue when coughing or sneezing, discard tissue immediately in a closed bin, and wash hands).
- Inform your TB doctor if you develop new symptoms such as fever, a cough, a change in your intensity of cough or difficulty breathing.
- All endTB trial participants should practice social distancing by staying at home and doing only essential actives during the outbreak of COVID-19.
- Many cities where the endTB trial is occurring have mandatory stay at home advisories; endTB trial participants are advised to strictly adhere to these measures as it can be a matter of life or death for them.

Annex 2. Nasopharyngeal Sampling (adapted from MSF)

Safety

- Health care workers collecting NP and OP swab specimens from suspected or confirmed COVID-19 patients should be well-trained on the procedure.
- A clean, non-sterile, long-sleeve gown, a respirator, eye protection (i.e., goggles or face shield), and gloves should be worn.
- Procedure should be conducted in a separate/isolation room, and during NP specimen collection health care workers should request the patients to cover their mouth with a medical mask or tissue.
- Although collection of NP and OP swabs have the potential to induce fits of coughing from the patient undergoing the procedure, there is no currently available evidence that cough generated via NP/OP specimen collection leads to increased risk of COVID-19 transmission via aerosols.

Equipment

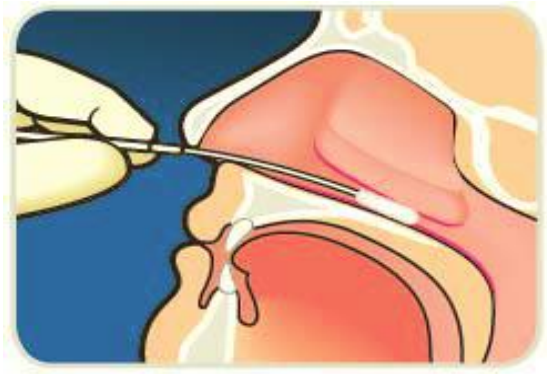
- Tube UTM (Universal Transport Media) 3ml + 2 swabs flocked tip, plastic flex stick (oral swab + nasopharyngeal swab).

Please note that if none of these references are available:

- Prioritize nasal swab (higher viral load).
- WHO accepts lower volumes of UTM (1 and 2 ml).

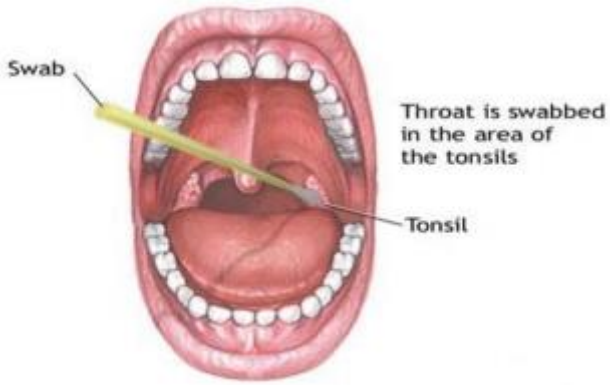
Procedure

1. Identify the tube with the patient's name and the location, date and time of collection.
2. Seat the patient comfortably.
3. **Nasopharyngeal swab**:
    - Tilt the head back and insert the nasal swab carefully parallel to the floor of nose without pointing upwards until resistance is felt.
    - Rotate the swab on the nasopharyngeal membrane a few times, remove it carefully and insert it into the UTM
    - Break off the top part of the stick and tighten the screw cap firmly.

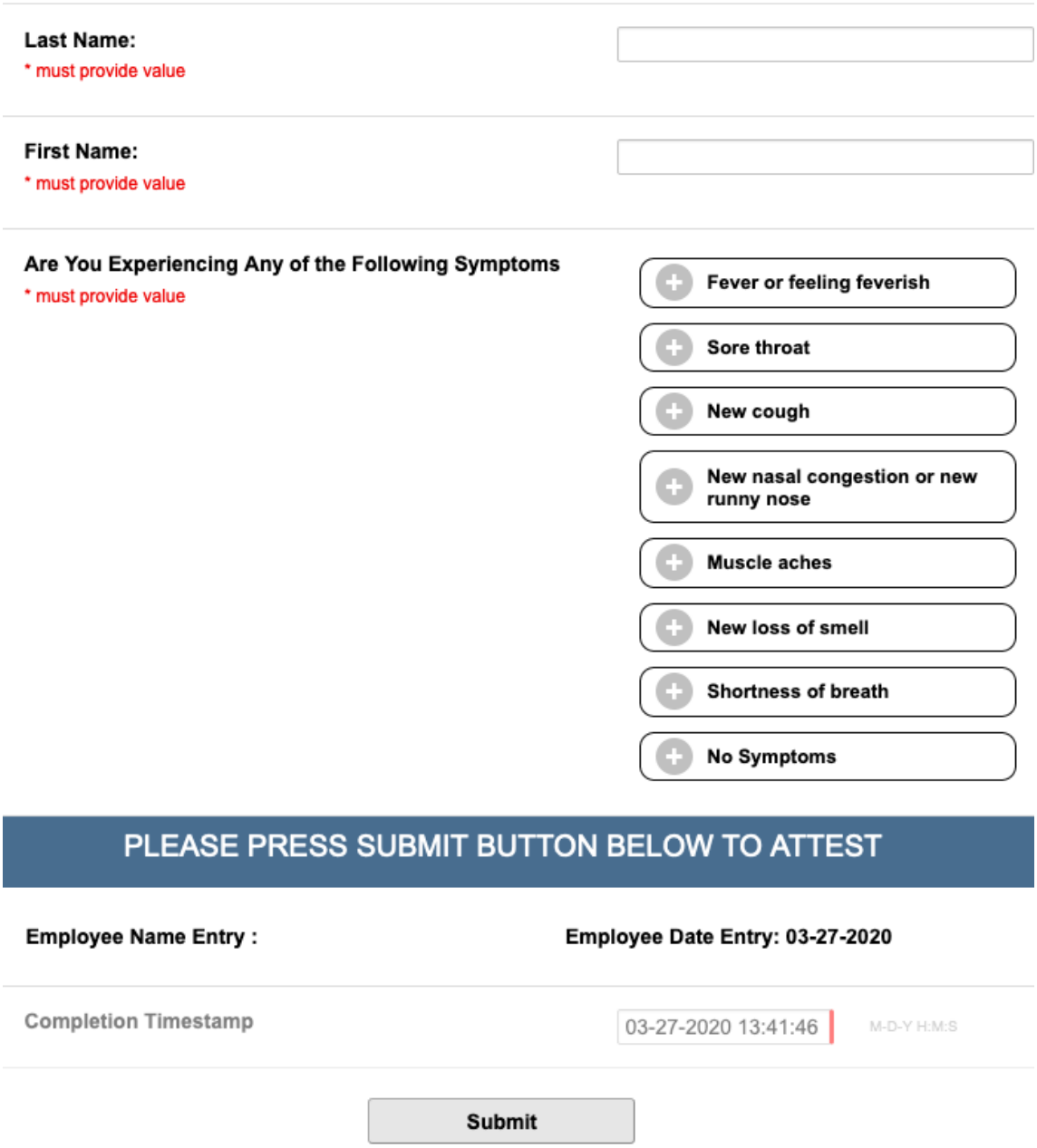


Oropharyngeal swab:

- Insert the second swab in the mouth;
- Swab the posterior pharynx and tonsillar areas (avoid the tongue);
- Place tip of swab in the same UTM with NP swab and cut off the applicator tip.



Annex 3. Example of self-screening questionnaire (from Brigham and women)



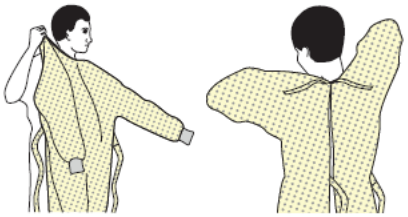
Annex 4. How to put and remove PPE (CDC)

SEQUENCE FOR PUTTING ON PERSONAL PROTECTIVE EQUIPMENT (PPE)

The type of PPE used will vary based on the level of precautions required, such as standard and contact, droplet or airborne infection isolation precautions. The procedure for putting on and removing PPE should be tailored to the specific type of PPE.

1. GOWN

- Fully cover torso from neck to knees, arms to end of wrists, and wrap around the back
- Fasten in back of neck and waist



2. MASK OR RESPIRATOR

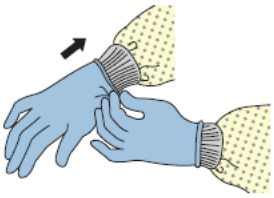
- Secure ties or elastic bands at middle of head and neck
- Fit flexible band to nose bridge
- Fit snug to face and below chin
- Fit-check respirator

3. GOGGLES OR FACE SHIELD

- Place over face and eyes and adjust to fit

4. GLOVES

- Extend to cover wrist of isolation gown



USE SAFE WORK PRACTICES TO PROTECT YOURSELF AND LIMIT THE SPREAD OF CONTAMINATION

- Keep hands away from face
- Limit surfaces touched
- Change gloves when torn or heavily contaminated
- Perform hand hygiene

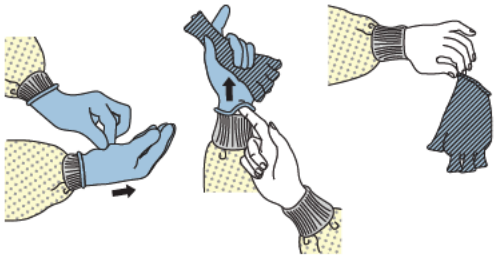
CS250672-E

HOW TO SAFELY REMOVE PERSONAL PROTECTIVE EQUIPMENT (PPE) EXAMPLE 1

There are a variety of ways to safely remove PPE without contaminating your clothing, skin, or mucous membranes with potentially infectious materials. Here is one example. **Remove all PPE before exiting the patient room** except a respirator, if worn. Remove the respirator **after** leaving the patient room and closing the door. Remove PPE in the following sequence:

1. GLOVES

- Outside of gloves are contaminated!
- If your hands get contaminated during glove removal, immediately wash your hands or use an alcohol-based hand sanitizer
- Using a gloved hand, grasp the palm area of the other gloved hand and peel off first glove
- Hold removed glove in gloved hand
- Slide fingers of ungloved hand under remaining glove at wrist and peel off second glove over first glove
- Discard gloves in a waste container



2. GOGGLES OR FACE SHIELD

- Outside of goggles or face shield are contaminated!
- If your hands get contaminated during goggle or face shield removal, immediately wash your hands or use an alcohol-based hand sanitizer
- Remove goggles or face shield from the back by lifting head band or ear pieces
- If the item is reusable, place in designated receptacle for reprocessing. Otherwise, discard in a waste container

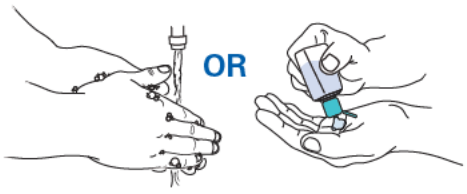
3. GOWN

- Gown front and sleeves are contaminated!
- If your hands get contaminated during gown removal, immediately wash your hands or use an alcohol-based hand sanitizer
- Unfasten gown ties, taking care that sleeves don't contact your body when reaching for ties
- Pull gown away from neck and shoulders, touching inside of gown only
- Turn gown inside out
- Fold or roll into a bundle and discard in a waste container

4. MASK OR RESPIRATOR

- Front of mask/respirator is contaminated — DO NOT TOUCH!
- If your hands get contaminated during mask/respirator removal, immediately wash your hands or use an alcohol-based hand sanitizer
- Grasp bottom ties or elastics of the mask/respirator, then the ones at the top, and remove without touching the front
- Discard in a waste container

5. WASH HANDS OR USE AN ALCOHOL-BASED HAND SANITIZER IMMEDIATELY AFTER REMOVING ALL PPE



PERFORM HAND HYGIENE BETWEEN STEPS IF HANDS BECOME CONTAMINATED AND IMMEDIATELY AFTER REMOVING ALL PPE

CS250672-E

Annex 5. Screening and secondary prevention

- Early case detection through screening or contact tracing is an excellent way to prevent further spread (see Chapter 4 for more on contact tracing).
- People who may have been exposed to individuals with suspected COVID-19 (including healthcare workers) should be advised to monitor their health for 14 days (using the screening tool in section annex) from the last day of possible contact, and seek immediate medical attention if they develop any symptoms, particularly fever, respiratory symptoms such as coughing or shortness of breath, or diarrhea.
- Local health authorities may request that people enter into voluntary quarantine (staying at home and avoiding contact with other people for 14 days) depending on their risk of exposure.
- Symptomatic or confirmed COVID-19 patients should wear a surgical mask while waiting in triage or waiting areas or during transportation out of isolation. If medical masks are in short supply, they should cover their mouths with a piece of (cotton) cloth.

Annex 6. Screening health care workers in high COVID-19 patient flow areas

- Prevalence studies of infection in groups can be done by testing for the presence of antibodies using the antibody (IgM/IgG) test; to date there have not been many studies done as they are resource intensive.
- This guide does not cover how to do prevalence studies.
- As part of surveillance of health staff working with endTB patients, a surveillance of health workers in the unit may be done for the presence of COVID-19 antibodies. For example, 10% of the nurses working on an inpatient ward could be tested periodically.

Annex 7. Privacy Recommendations for endTB site staff in COVID-19 pandemic

In the context of the COVID-19 pandemic, you do have restricted if ever no physical access to the office, hospitals wards or to patients' home. Your professional activities are in consequence deeply impacted. We're grateful for the efforts deployed in these circumstances to maintain the endTB activities and to ensure patients' follow-up. However as you're handling patient's health information, personal and highly sensitive: there is a need to carefully use and share it for preventing any misuse and harm to patients and their communities.
In order to ensure the security of patients' information and their confidentiality, MSF as endTB study Sponsor would like to provide you with the following basic recommendations, based on fundamental data protection principles as defined in the attached MSF Health Data Protection Infographic.

TIPS FOR HOMEWORK RESORTING MOBILE DEVICE

Here are the basic data security measures to access the endTB studies' tools e.g. SharePoint, OpenClinica, e-mails, Vennlife, ERT portal:

- ✓ Ensure your device has the most up-to-date software and anti-virus, and is protected by a strong password.
- ✓ Do not use shared or public computers to access endTB information, do not connect to public WIFI.
- ✓ Stay vigilant against phishing attempts, do not to open any emails or attachments that seem suspicious.
- ✓ Do not let anyone access your devices and professional applications, do not leave your device unattended or unlocked at any time.
- ✓ Do not share any of your login credentials.
- ✓ Do not use your personal device alike your phone for work purposes. If not feasible, ensure your device comply with the above data security measures.
- ✓ Do not use your personal email address.
- ✓ **Do not use other applications or social media** like WhatsApp, Google drive, Facebook, messengers….
- ✓ Do not store patients information on endTB non-supported repositories like Dropbox, or private device (phone, mobile devices).
- ✓ **Delete, erase, retrieve the scans, photos, pictures and any patients related information stored in your mobile device including your phone' memory, in storage places, attachments, in SMS.**
- ✓ Do not leave paper copies containing Personal Data unattended and accessible.
- ✓ Do not forget to check your local IT security guidelines. Avoid whenever possible the storage on USB keys or external hard drive, unless they are encrypted.

FOR ANY REQUESTS AND ISSUES: YOU CAN CONTACT DIRECLTY YOUR CENTRAL SUTDY COORDINATOR

FOR THE COLLECTION, USE, SHARING, TRANSFER OR STORING OF endTB PATIENTS INFORMATION&DATA

E.g. sharing Patients worksheet from medical doctor to Data Entry staff or to the authorized Internal Monitors, you should:

- ✓ Use your professional device and your professional login/password to connect you and protect your credentials, use secure and authorized endTB tools, applications and servers.
  → **Security: see the measures above**
- ✓ Collect, share and store only what is strictly necessary to the endTB patients' follow up.
  → **Data Minimization**
- ✓ Refrain from collecting or sharing any data in the first place that puts patients at unnecessary risk. Remember you handle sensitive data: i.e. the benefit of the extra information must be proportionate to the risk to patients.
  → **Proportionality & Do No Harm**
- ✓ De-identify as much as you can the information you handle and share and use the unique endTB patients ID: remove direct names, ages, address or location or any direct identifying/individual information.
  → **Anonymization & Pseudonimization**
- ✓ Respect the medical confidentiality i.e. information covered by medical confidentiality can only be shared with those directly involved in the patient's treatment & follow up with patient consent: i.e. the site coordination team, the investigation doctor, the data entry manager and the Internal Monitors.
  → **Medical Ethics**

References

[1] Yongyu Liu, Lijun Bi, Yu Chen, Yaguo Wang, Joy Fleming, Yanhong Yu, Ye Gu, Chang Liu, Lichao Fan, Xiaodan Wang, Moxin Cheng: Active or latent tuberculosis increases susceptibility to COVID-19 and disease severity. medRxiv 2020.03.10.20033795;doi: https://doi.org/10.1101/2020.03.10.20033795

[2] WHO: Global TB progress at risk. 14 October 2020. https://www.who.int/news/item/14-10-2020-who-global-tb-progress-at-risk

[3] CDC interim guidelines, updated May 5, 2020

[4] Public Health England. Guidance COVID-19: laboratory investigations and sample requirements for diagnosis Updated 11 May 2020. https://www.gov.uk/government/publications/wuhan-novel-coronavirus-guidance-for-clinical-diagnostic-laboratories/laboratory-investigations-and-sample-requirements-for-diagnosing-and-monitoring-wn-cov-infection

[5] Centers for Disease Control and Prevention (CDC). Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens from Persons for Coronavirus Disease 2019 (COVID-19). Updated May 5, 2020. https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html

[6] US FDA. Coronavirus (COVID-19) Update: Daily Roundup. March 23, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup

[7] WHO Emergency Use Assessment Coronavirus disease (COVID-19).IVDs. July 2020. https://www.who.int/diagnostics_laboratory/eual/200724_final_pqpr_eul_0511_070_00_xpert_xpress.pdf?ua=1

[8] World Health Organization. Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays. 2020; (September). https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays

[9] FIND Evaluation of Bionote, Inc. NowCheck COVID-19 Ag Test External Report Version 1.0, 18 September 2020. https://www.finddx.org/wp-content/uploads/2020/09/Bionote_Ag-INTERIM-Public-Report_20200918.pdf

[10] FIND Evaluation of SD Biosensor, Inc. STANDARD Q COVID-19 Ag Test External Report Version 1.0, 18 September 2020. https://www.finddx.org/wp-content/uploads/2020/09/SDQ-Ag-Public-Report_20200918.pdf

[11] WHO Emergency Use Listing for In vitro diagnostics (IVDs) Detecting SARS-CoV-2. https://www.who.int/diagnostics_laboratory/201002_eul_sars_cov2_product_list.pdf

[12] Nisreen M.A., Muller MA, Li W, Wang C, et al. SARS-CoV-2 specific antibody responses in COVID-19 patients. medRxiv preprint doi: https://doi.org/10.1101/2020.03.18.20038059

[13] FIND evaluation of SARS-CoV-2 antibody (Ab) detection tests. https://www.finddx.org/covid-19/sarscov2-eval-antibody/

[14] Diagnostic testing for SARS-CoV-2 Interim guidance. 11 September 2020. https://www.who.int/publications/i/item/diagnostic-testing-for-sars-cov-2

[15] Rodino KG, Espy MJ, Buckwalter SP, Walchak RC, Germer JJ, Fernholz E, Boerger A, Schuetz AN, Yao JD, Binnicker MJ. Evaluation of saline, phosphate buffered saline and minimum essential medium as potential alternatives to viral transport media for SARS-CoV-2 testing. J Clin Microbiol. 2020 Mar 30.

[16] Rogers AA, Baumann RE, Borillo GA, Kagan RM, Batterman HJ, Galdzicka M, Marlowe EM. Evaluation of Transport Media and Specimen Transport Conditions for the Detection of SARS-CoV-2 Using Real Time Reverse Transcription PCR. J Clin Microbiol. 2020 Apr 27.

[17] Galluccio F, Fajardo M. http://www.rheumapainacademy.com/wp-content/uploads/2020/03/algoritmo-28.03.pdf (accessed on April 4th, 2020).

[18] https://www.gilead.com/-/media/files/pdfs/remdesivir/eua-fact-sheet-for-hcps_01may2020.pdf

[19] Beigel et al, Remdesivir for the Treatment of Covid-19 — Preliminary Report, NEJM 2020.

[20] Spinner et al, Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19. JAMA 2020.

[21] Grein J[1], Ohmagari N[1], Shin D[1],et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med. 2020 Apr 10. doi: 10.1056/NEJMoa2007016.

[22] Wang et al, Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet. 2020 April 29. https://doi.org/10.1016/S0140-6736(20)31022-9

[23] Goldman et al, Remdesivir for 5 or 10 Days in Patients with Severe Covid-19, NEJM 2020.

[24] WHO. Therapeutics and COVID-19. Living Guidelline. 20 November 2020. Last accessed 23 Nov 2020. https://www.who.int/publications/i/item/therapeutics-and-covid-19-living-guideline

[25] Chen Jun,Liu Danping,Liu Li,et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *J Zhejiang Univ (Med Sci)*, 2020, 49(1): 0-0. http://www.zjujournals.com/med/EN/10.3785/j.issn.1008-9292.2020.03.03

[26] Molina JM, Delaugerre C, Goff JL, Mela-Lima B, Ponscarme D, Goldwirt L, de Castro N, No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection, *Médecine et Maladies Infectieuses* (2020), doi: https://doi.org/10.1016/j.medmal.2020.03.006.

[27] Geleris et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020 May 7. doi: 10.1056/NEJMoa2012410.

[28] Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State.JAMA. 2020 May 11. doi: 10.1001/jama.2020.8630.

[29] Horby et al, Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. medRXiv 2020; WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19. https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19

[30] Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020 Mar 18.

[31] Chang Chen, Yi Zhang, Jianying Huang, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. MedRxiv. April 15, 2020 doi: https://doi.org/10.1101/2020.03.17.20037432

[32] Gautret P[1], Lagier JC[2], Parola P[1],et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020 Mar 20:105949. doi: 10.1016/j.ijantimicag.2020.105949

[33] Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. Am J Respir Crit Care Med. 2018;197(6):757-767. doi: 10.1164/rccm.201706-1172OC. PMID: 29161116.

[34] Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med. 2006;3(9):e343. Epub 2006/09/14. doi: 10.1371/journal.pmed.0030343. PubMed PMID: 16968120; PMCID: PMC1564166.

[35] Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020 Mar;8(3):267-276. doi: 10.1016/S2213-2600(19)30417-5. Epub 2020 Feb 7. PMID: 32043986.

[36] The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. NEJM 2020.

[37] The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19. JAMA 2020.

[38] Regeneron and Sanofi Provide Update on Kevzara® (sarilumab) Phase 3 U.S. Trial in COVID-19 Patients. https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-and-sanofi-provide-update-kevzarar-sarilumab-phase-3/

[39] Nadkami et al. Anticoagulation, Mortality, Bleeding and Pathology Among Patients Hospitalized with COVID-19: A Single Health System Study. JACC 2020.

[40] World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance. 13 March 2020. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

[41] World Health Organization. Global surveillance for COVID-19 caused by human infection with COVID-19 virus. Interim guidance. 20 March 2020. https://apps.who.int/iris/handle/10665/331506

[42] World Health Organization. Global surveillance for COVID-19 caused by human infection with COVID-19 virus. Interim guidance. 20 March 2020.https://apps.who.int/iris/handle/10665/331506

[43] World Health Organization. Rational use of personal protective equipment for coronavirus disease (COVID-19) and considerations during severe shortages: interim guidance, 6 April 2020. World Health Organization. https://apps.who.int/iris/handle/10665/331695. License: CC BY-NC-SA 3.0 IGO

[44] Centers for Disease Control and Prevention (CDC). (2020). Standard Precautions for All Patient Care. https://www.cdc.gov/infectioncontrol/basics/standard-precautions.html

[45] CDC. Discontinuation of Isolation for Persons with COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-in-home-patients.html

[46] World Health Organization. (2020). Rational use of personal protective equipment for coronavirus disease (COVID-19) and considerations during severe shortages: interim guidance, 6 April 2020. World Health Organization. https://apps.who.int/iris/handle/10665/331695. License: CC BY-NC-SA 3.0 IGO

[47] World Health Organization. (2020). Advice on the use of masks in the context of COVID-19: interim guidance, 6 April 2020. World Health Organization. https://apps.who.int/iris/handle/10665/331693. License: CC BY-NC-SA 3.0 IGO

[48] Centers for Disease Control and Prevention (CDC). Evaluating and Testing Persons for Coronavirus Disease 2019 (COVID-19)

[49] PIH Guide to PPE conservation 2020

[50] Centers for Disease Control and Prevention (CDC). NIOSH. Recommended Guidance for Extended Use and Limited Reuse of N95 Filtering Facepiece Respirators in Healthcare Settings.

[51] Fisher, E.M., and R.E. Shaffer: Considerations for Recommending Extended Use and Limited Reuse of Filtering Facepiece Respirators in Healthcare Settings *Journal of Occupational and Environmental Hygiene*: (in press) (2014).

[52] Bergman, M.S., D.J. Viscusi, Z. Zhuang, A.J. Palmiero, J.B. Powell, and R.E. Shaffer: Impact of multiple consecutive donnings on filtering facepiece respirator fit. *American Journal of Infection Control* 40(4): 375-380 (2012).

[53] WHO. Tips for health and safety at the workplace in the context of COVID-19. https://www.who.int/news-room/q-a-detail/q-a-tips-for-health-and-safety-at-the-workplace-in-the-context-of-covid-19?gclid=EAIaIQobChMIxauRib-g6wIVl53VCh1GGg-0EAAYAiAAEgKqfvD_BwE