The endTB COVID-19 Response

Interim Guidance for the endTB Trial sites

Version 1.1

Updated 12 May 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.

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

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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.

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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
PEEP	Positive end-expiratory pressure
PIH	Partners In Health
PO	Per os
POC	Point of care
PPE	Personal protective equipment
PPV	Positive predictive value
PUI	Person under investigation
RDT	Rapid diagnostic test
RH	Relative humidity
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.
- 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 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

- The reference test in use for the detection of SARS-CoV-2 infection and disease is:
  - **Reverse transcription polymerase chain reaction (RT-PCR).**
- There are two types of Rapid Diagnostic Tests (RDTs) that are available:
  - **Antibody (IgM/IgG) rapid diagnostic test (Ab-RDT); and**
  - **Antigen rapid diagnostic test (Ag-RDT).**

  At present, endTB partners are still reviewing the performance of the different RDTs from different manufacturers. Whether the RDTs can play a role in a COVID-19 outbreak, especially when RT-PCR is not available, is still under evaluation.
- 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.
- Lung ultrasound can also be helpful and shows a characteristic finding of a diffuse B-pattern.
- Table 2.1 summarizes the different diagnostic laboratory tests for COVID-19.

Table 2.1. Types of tests

Characteristic	RT-PCR	Antibody (IgM/IgG) RDT	Antigen (Ag) (RDT)
Sample	Nasopharyngeal swab or deep sputum[2,3]	Blood (finger stick or blood draw)	Nasopharyngeal swab or deep sputum
Window period	Short	5-7 days	Short
False positives	Almost none	**Low** (if pretest probability is high) **Medium** (if pretest probability is low)	Almost none
False negatives	Occasionally (especially in the window period)	Variable. High at the onset of the disease	**High**
Turn-around time	Hours	15 min	15 min

Reverse transcription polymerase chain reaction (RT-PCR)

- **RT-PCR is the test of choice for detecting SARS-CoV-2 in the endTB COVID-19 response.**
- RT-PCR detects the genetic RNA within the virus particles.
- The most commonly used sample for RT-PCR is the nasopharyngeal swab.
- Testing lower respiratory tract specimens for SARS-CoV-2 is an acceptable option in patients who have a productive cough.[4,5] It may be the preferred option in a TB patient that has productive cough to decrease the number of different specimens being collected.
- Sputum induction techniques should be avoided because of the risk of aerosols exposure.

- 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.[6]
- The role of using saliva instead of a nasopharyngeal swab is being explored and shows promising results (see section c. below and Annex 2 for more information).
- A nasopharyngeal swab is taken from deep in the nose (see Annex 3).
- The nasopharyngeal swab can be self-administered[7] 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 is highly specific, which means the chance of a false positive is very low.
- The RT-PCR test may have a sensitivity of around 75%, which means false negatives can occur, mostly within the window period.
- There is a window period at the start of the onset of symptoms when the patient may test RT-PCR negative but has the disease. The window period is due to a low viral load that makes the virus not detectable.
- Therefore, if the RT-PCR is negative but suspicion for COVID-19 remains, then ongoing quarantine (see definition p. 27) and re-testing several days later should be considered (see figure 2.2).
- 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 US FDA Emergency Use Authorization.[8] It is anticipated that the cartridge will not be available outside the USA until late June/early July 2020. The endTB consortium is strongly considering using the Xpert® Xpress SARS-CoV-2 cartridge as a method of testing, but other methods will have to be used until it can be procured. 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.

Rapid Diagnostic Tests

endTB partners are examining different Rapid Diagnostic tests (RDTs). RDTs are not as accurate as PCR but have the advantage of being simple to perform, rapid point of care (POC) tests and are less costly than RT-PCR. Their role in case detection is still to be clarified. No RDT should be used before independent evaluation of its performance against the RT-PCR. Such studies are already on-going and could be considered in some sites. Only stringent regulatory authority (SRA) registered tests should be considered (see Annex 4).

Antigen (Ag) RDTs

- These tests are done on a sputum specimen or nasopharyngeal swab.
- The tests detect protein “antigens” on the virus, not the genetic material.
- Currently available Ag tests have a low sensitivity and a good specificity. Patients with a negative antigen result have to be retested by RT-PCR. At present, antigen tests alone cannot be used to rule out COVID-19 disease.

- Separate instructions will be forthcoming in future versions of this document (see Annex 5).

Antibody (Ab) RDTs

- These tests are done on blood (finger stick or blood draw).
- Sensitivity and specificity vary widely depending on the brand of antibody test.[9] There is a general lack of evidence on performance and it is difficult to know how to choose from among numerous companies.
- The lag time of antibodies creates a window period during which the patient may have a negative antibody RDT, but still have COVID-19. Antibody response is also variable among individuals (age, symptoms, etc.). In general, IgM is indicative of acute infection and can be detected in most patients 7 days after the onset of symptoms, and IgG becomes positive a few days after the rise of IgM (see Annex 6) and can remain elevated after the infection has resolved.
- To decrease the number of false negatives, use the antibody test a minimum of 7 days after the onset of symptoms such as fever. Antibody tests are therefore not recommended for the early detection of the disease which limits its interest in case management and isolation.
- Antibody tests can inform the circulation of the virus in a population (e.g., HCW, see Annex 7) but have no clear role in the detection of cases.
- Antibody tests can also inform if there has been a past infection with SARS-CoV-2 (see Annex 7).

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 2.2.
- Figure 2.2 illustrates the persons to be tested and the endTB recommended testing algorithm.

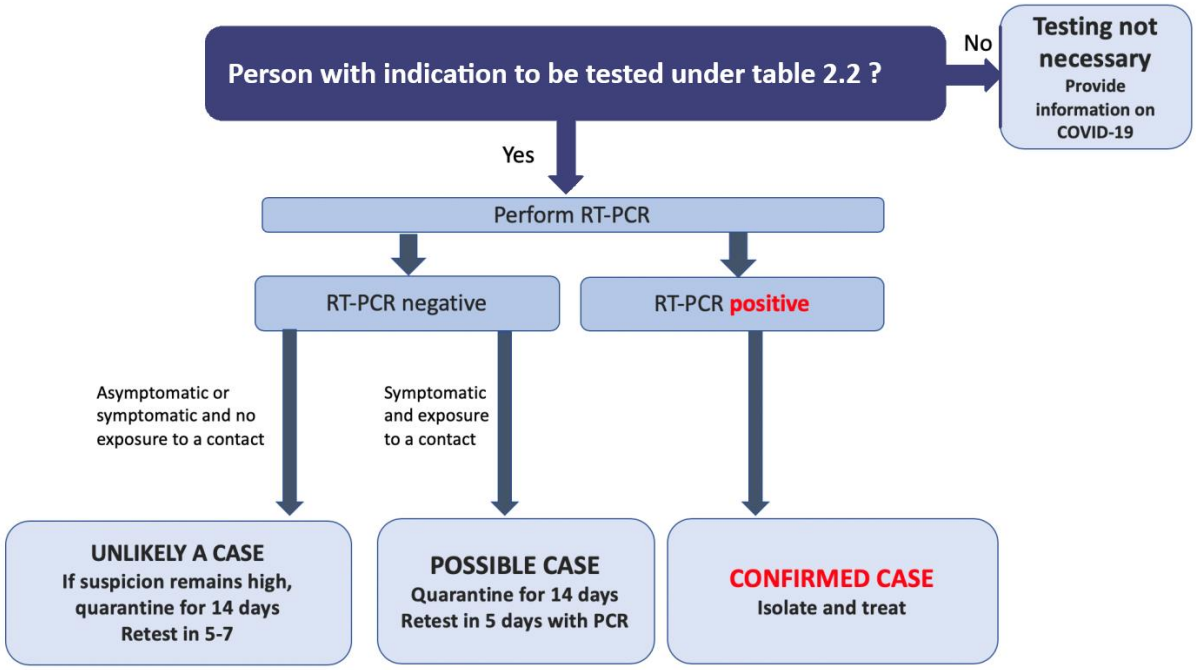
Table 2.2 Persons to be tested for COVID-19

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 8).

Figure 2.2 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 2.2.
- All HH contacts of the study participants will be tested under the circumstances of Table 2.2.

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. As stated above, sputum can be used in patients with a productive cough. There would be many advantages if the testing of saliva could be used. There are several small studies that examine whether saliva can be used to detect SARS-CoV-2, and the results are quite encouraging, see Annex 2.

This guide does not endorse the use of saliva over nasopharyngeal specimens until further studies are published. At this time, using saliva specimens should only be done if nasal swabs are not available and the patient is not able to produce sputum[4,5]. This guide will be updated on the use of saliva.

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.[10,11] 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.

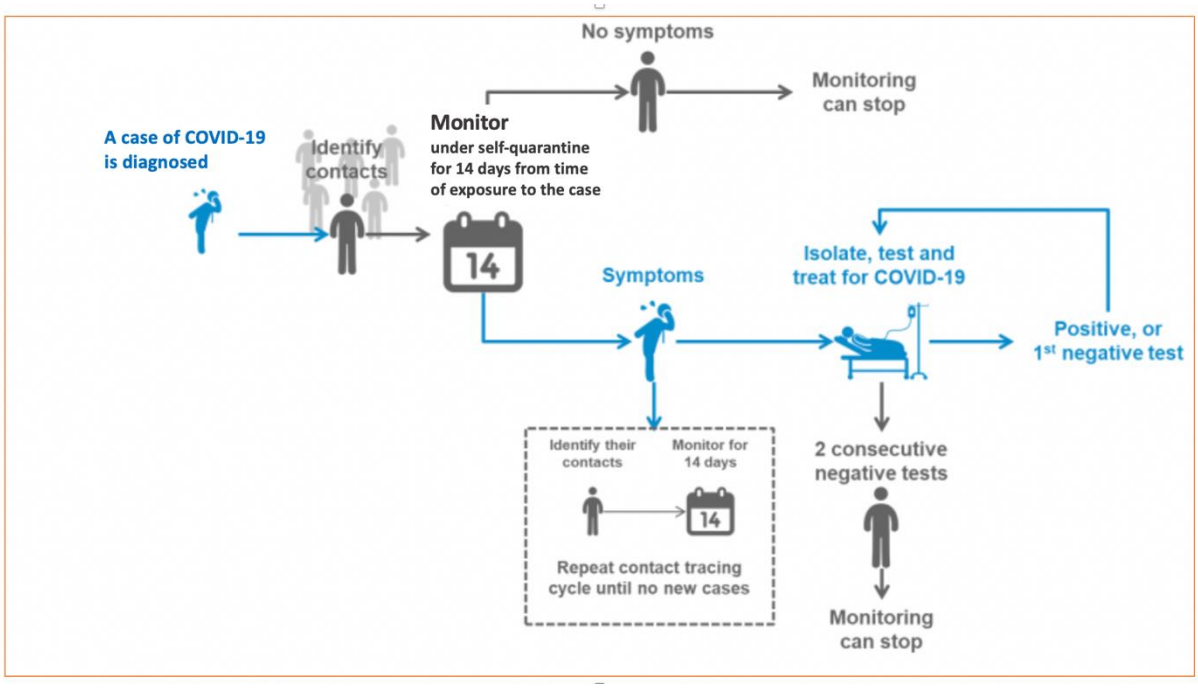
e. Procurement, ordering and forecasting of COVID-19 tests

- 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.

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)

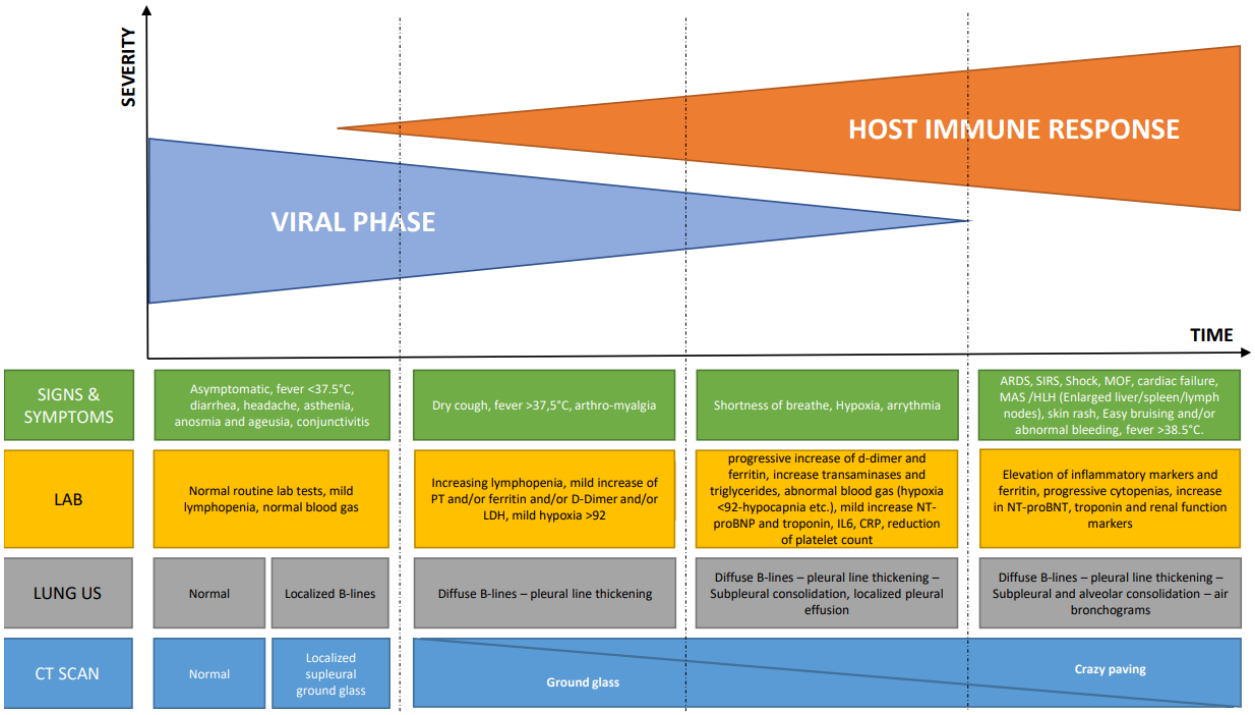


4. Treatment

At the time of this writing there are no 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 or protease inhibitors) in the first phase, followed by immunomodulatory drugs (e.g., tocilizumab or corticosteroids) to control the hyper-inflammatory response in the second phase of the disease. Some drugs, like hydroxychloroquine, might play a role during both phases of the disease.

Figure 4.1. Clinical, instrumental and pathogenetic model of COVID-19. Modified from Galluccio et al.[12]



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)	To date, little evidence is available on the efficacy of remdesivir to treat COVID-19. On 01 May 2020, the U.S. FDA issued an Emergency Use Authorization[13] for remdesivir based on unpublished preliminary results of the ACTT trial (ClinicalTrials.gov NCT04280705). Other available evidence for remdesivir includes: a) an uncontrolled trial showing overall good safety results,[14] b) a randomized controlled trial which was stopped early for insufficient recruitment and did not show superiority of remdesivir towards placebo,[15] and c) unpublished preliminary results that show similar outcomes in patients receiving 5 and 10 days of remdesivir.[16] 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)	Of note, initial studies supporting the use of hydroxychloroquine were observational and conducted on limited number of participants.[29] These findings have not been confirmed by recent reports, including two recently-published large retrospective studies.[17,18,19,20] On March 28, 2020, the U.S. FDA issued an Emergency Use Authorization for hydroxychloroquine and chloroquine.[21] Modelling studies suggest that higher doses than the commonly used posology (below) may be more effective.[22,23,24] Chloroquine may be used as an alternative to hydroxychloroquine, although this drug appears to have a worse safety profile. Of note, high doses of chloroquine have been associated with cardiac toxicity.[25] Posology: (hydroxychloroquine) 2 capsules twice daily for 1 day (loading dose), followed by 1 capsule twice daily. Total treatment duration is unclear. 5 days have been proposed for symptomatic forms without signs of severity.[26] For severe COVID-19, longer treatment duration (up to three weeks) may be indicated. (chloroquine) 6 capsules once (loading dose), then 3 capsules twice daily until day 5.
Boosted protease inhibitors (lopinavir/ritonavir (200/50 mg), darunavir (800 mg) plus ritonavir	Of note, very 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.[27] Posology: (lopinavir/ritonavir) 2 capsules twice daily for 7 days. Treatment duration

(100 mg), darunavir/cobicistat (800/150 mg))	of 14 days has been proposed. (darunavir plus ritonavir) 1 capsule darunavir + 1 capsule ritonavir daily for 7 days. (darunavir/cobicistat) 1 capsule/day for 7 days.
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.[28] 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,[29] which has not been confirmed in a large retrospective study.[20] 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. At the time of writing this guide there is no clear evidence of their efficacy.

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

Drugs	Available evidence and posology
Corticosteroids	The use of corticosteroids in COVID-19 is controversial. Studies have shown no benefit associated with their use in the treatment of disease caused by SARS-CoV-1 and MERS-CoV.[30,31] However, a recent randomized controlled clinical trial has found that dexamethasone could reduce mortality among patients with moderate-to-severe ARDS.[32] Therefore, the use of corticosteroids could be considered in severe COVID-19 cases (with or without ARDS) with signs of hyper-inflammatory ("cytokine storm") 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). Posology: The following treatment scheme may be employed: Dexamethasone IV 20 mg daily for 5 days, followed by 10 mg daily for 5 days.
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). 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 dosage of 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 critically-ill patients with high levels of D-dimer, increased inflammatory markers, and/or multiorgan failure.

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. If possible, participation to clinical research should be encouraged. If participation to clinical research is not possible, the following elements could be considered:

- Patients with symptomatic, confirmed COVID-19[33] and risk factors for unfavorable outcome* are likely to benefit from treatment in most cases;
- Patients with symptomatic, confirmed COVID-19 but without risk factors for unfavorable outcome* may benefit from treatment, depending on drug availability and on risk of additive toxicity/interaction with other treatments the patient is taking;

- Patient with severe COVID-19 pneumonia[34] with/without acute respiratory distress syndrome are most likely to benefit from treatment, except for specific individual contraindications.

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	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

and COVID-19	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.[35]

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.[36]

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 8. 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.

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) [37,38]

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			
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)[39]

[b] When performing aerosol generating procedures (e.g. tracheal intubation, non-invasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation, bronchoscopy)

A poster showing how to put and remove PPE is presented in Annex 9. 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[40,41,42]

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:[43]

- Respirators must be worn by a single wearer;
- Respirators must be put and removed following instructions (see Annex 9);
- 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[44,45] 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.

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.

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).

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. Use of sputum/saliva for collection of detection of SARS CoV-2

Evidence

- In one study, saliva was collected by asking the patient to cough out saliva from their throat into a sterile container. In the study 11 cases out of 12 (91.67%) of COVID-19 patients demonstrated SARS-CoV-2 in their saliva.[46]
- In another study, all patients were asked to produce an early morning saliva sample from the posterior oropharynx (i.e., coughed up by clearing the throat) before toothbrushing and breakfast. This was done because it is thought that nasopharyngeal secretions move posteriorly, and bronchopulmonary secretions move by ciliary activity to the posterior oropharyngeal area while the patients are in a supine position during sleep. The study showed that 20 cases out of 23 (86.96%) of COVID-19 patients demonstrated SARS-CoV-2 in their saliva.[47]
- In a third study, salivary samples of 25 COVID-19 patients were analyzed by RT-PCR. All the samples tested positive for the presence of SARS-CoV-2.[48]
- In an unpublished not yet peer-reviewed analysis, MicroGenDx performed validation work on sputum and saliva due to the nationwide shortage of nasopharyngeal swabs. The validation work showed that saliva specimens had 100 percent sensitivity and 100 percent specificity. In fact, they found saliva yielded greater detection sensitivity and consistency throughout the course of infection. Furthermore, the study reported less variability in self-sample collection of saliva.[49]

Advantages of using saliva over nasopharyngeal or oropharyngeal swabs

- The patient can easily be instructed to produce saliva and the process does not aerosolize viral particles. (Note, if collecting sputum or instructing the patient to cough up saliva from the back of the throat, this should be done in a well-ventilated area that does not risk infections to others – like a sputum collection booth).
- No specialized swabs (which are often in short demand) are needed.
- It may be more sensitive and better for monitoring the response to COVID-19 treatment and determining when the patient is no longer infectious.

Differences between sputum specimens collected for TB and sputum/saliva specimens collected for COVID-19

- Many persons with COVID-19 often do not have productive coughs, making it difficult for the patient to produce sputum in the manner in which it is obtained in most TB programs.
- Most of the data from COVID-19 testing is on specimens that the patient is asked to produce saliva coughed up from the back of the throat. This is different from the instructions given to suspected cases of TB where the patient is asked to cough phlegm from the lung if possible. Specimens that contain only saliva are rejected for TB diagnosis, but note these specimens are acceptable for diagnosis of COVID-19.

- It is also believed that it is easier to extract RNA from saliva than to get it out of mucus materials. Saliva may have a higher load of the viral RNA than in mucus material (although this has not been properly studied).
- If the patient is able to produce phlegm from the lung the specimen is likely to have a high viral load,[50] although comparisons of deep sputum specimens versus saliva produced from the back of the throat have not been done.
- U.S. CDC guidelines for processing of sputum specimens for SARS-CoV-2 RT-PCR recommend the use of dithiothreitol (DTT) for liquification of often viscous mucoid/mucopurulent material prior to nucleic acid extraction.[51] It is less likely although not yet fully studied whether salivary specimens will not require this additional step.
- In summary, saliva is a promising noninvasive method for specimen collection for diagnosis, monitoring, and infection control in patients with SARS-CoV-2 infection. Eliminating the need for the nasal swab would have many advantages. The main difference for TB and COVID-19 specimen collection is that a specimen that contains only saliva would be rejected as inadequate for TB but accepted in COVID-19. Saliva specimens may also require less reagents (i.e., DTT) to reduce mucoid viscosity when compared to sputum specimens.

Annex 3. 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

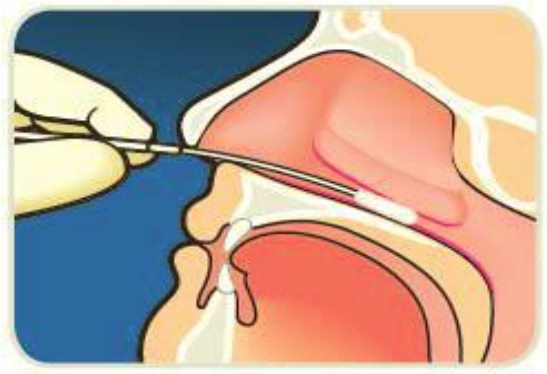
- Tube UTM (Universal Transport Media) 3ml + 2 swabs flocked tip, plastic flex stick (oral swab + nasopharyngeal swab).

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).

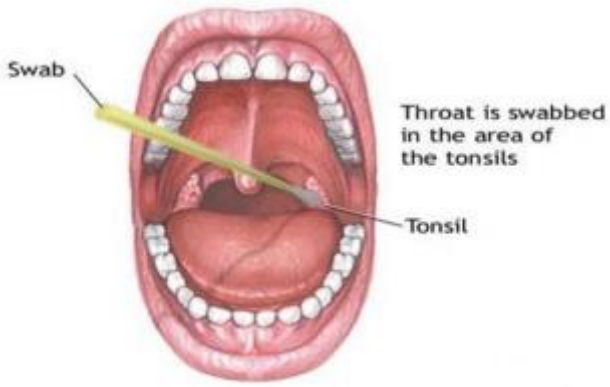
Procedure

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.

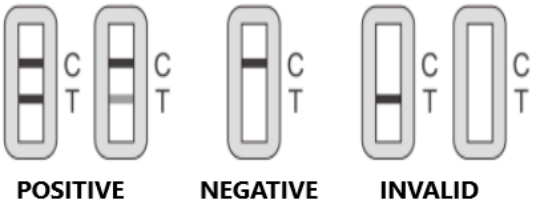


Annex 4. List of MSF approved Rapid Diagnostic Tests (RDT) for use only after validation against the RT-PCR

	Antibody RDTs			**Antigen RDTs**	
Test	2019-nCOV IgG/IgM Rapid Test Cassette	COVID-19 IgM, IgG, IgM/IgG rapid test	OnSite COVID-19 IgG/IgM Rapid Test	COVID-19 Respi-Strip Antigen Rapid test	Standard Q COVID-19 Ag
Company	Hangzhou AllTest Biotech Co. Ltd.	VivaCheck Biotech (Hangzhou) Co Ltd (China)	TK Biotech, Inc.(USA)	Coris Bioconcept (Belgium) *Clinical validation ongoing in Belgium*	SD BIOSENSOR, Inc. (Korea)

This list is not exhaustive and will be regularly updated.

Annex 5. Interpretation of results of the antigen test



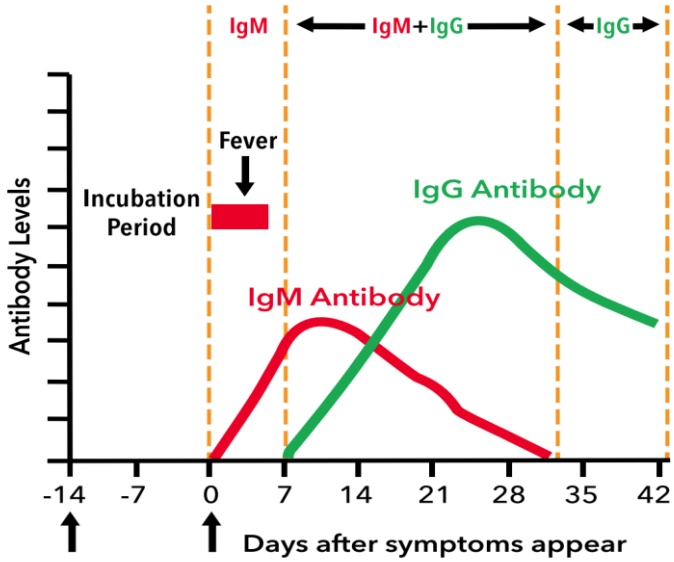
1. **Positive result:** Both the colored test band (T) and control band (C) appear on the membrane. Within the specified observation time, a very weak band should be judged as a positive result.

2. **Negative result:** Only the colored control band (C) appears on the membrane. The absence of the test band indicates a negative result.

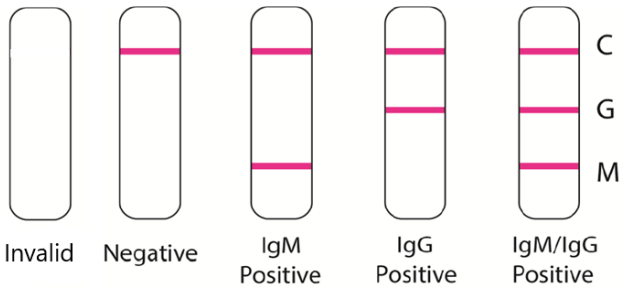
3. **Invalid result:** There should always be a colored control band in the control region regardless of test result. If control band is not seen, the test is considered invalid.

An invalid test can be due to an incorrect operation process. Possible reasons are discussed in separate testing SOPs and the test packaging insert.

Annex 6. The lag time between onset of symptoms and production of detectable antibodies



Annex 7. Interpretation of results of the antibody test



Three detection lines are possible, with the control (C) line appearing when sample has flowed through the cassette.

1. **Negative Result:** If only the quality control line (C) appears and the detection lines G and M are not visible, then no novel coronavirus antibody has been detected and the result is negative.

2. **Positive Result, M only**: If both the quality control line (C) and the detection line M appears, then the novel coronavirus IgM antibody has been detected and the result is positive for the IgM antibody. M only implies that the person is early in the infection.

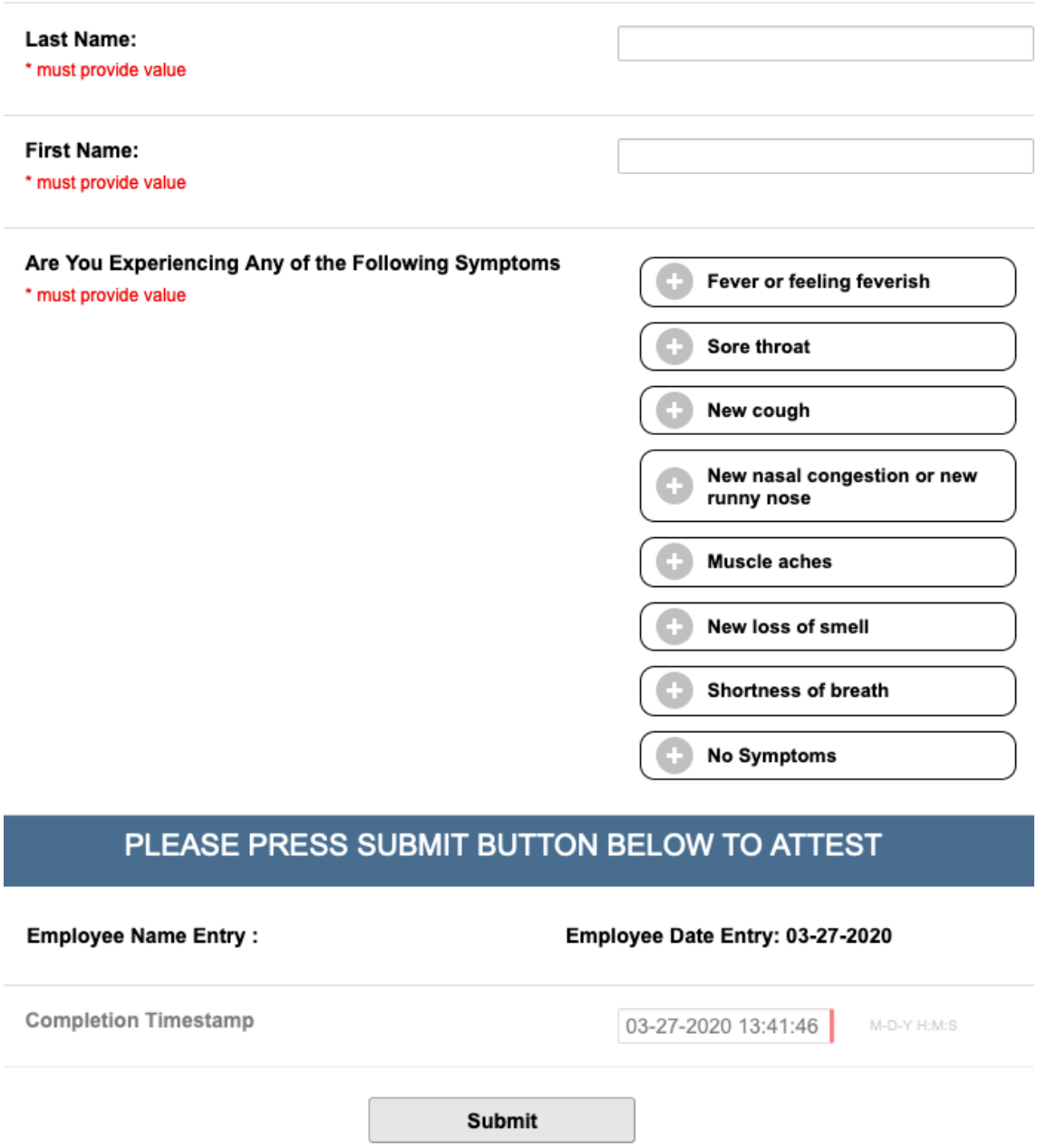
3. **Positive Result, G only**: If both the quality control line (C) and the detection line G appears, then the novel coronavirus IgG antibody has been detected and the result is positive for the IgG antibody. G only implies that the person is beyond the early phases of the infection.

4. **Positive Result, G and M**: If the quality control line (C) and both detection lines G and M appear, then the novel coronavirus IgG and IgM antibodies have been detected and the result is positive for both the IgG and IgM antibodies. Having both G and M implies the person is in the early to middle stages of infection.

5. **Positive result:** One or both the colored test band(s) (G and M) and control band (C) appear on the membrane. Within the specified observation time, a very weak test strip band should be judged as a positive result.

An invalid test can be due to an incorrect operation process. Possible reasons are discussed in separate testing SOPs and the test packaging insert.

Annex 8. Example of self-screening questionnaire (BWH)



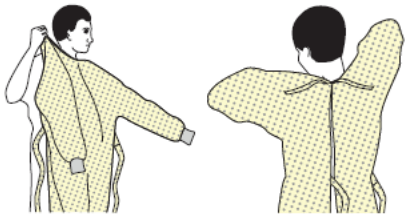
Annex 9. How to put and remove PPE (CDC)

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.

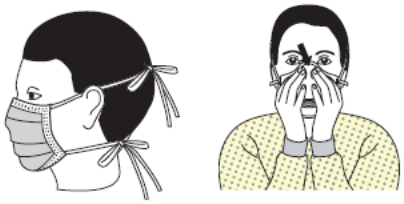
1. GOWN

- 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

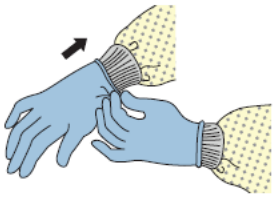


3. GOGGLES OR FACE SHIELD

- 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

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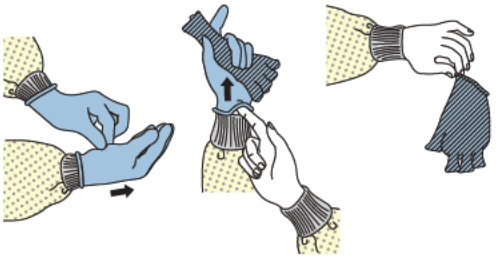
HOW TO SAFELY REMOVE PERSONAL PROTECTIVE EQUIPMENT (PPE) EXAMPLE 1

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

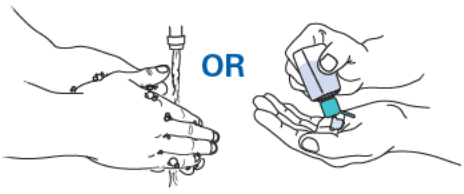
3. GOWN

- 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

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Annex 10. 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 11. 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 12. Current guidance on the use of drugs for COVID-19

Clinical Severity	France (HCSP/SPILF)	Italy (SIMIT)	US (covidprotocols.org)
Asymptomatic contact, negative test or test not done (=prophylaxis)	No treatment	No treatment	No treatment
Asymptomatic COVID-19 (positive test)	No treatment	No treatment	No treatment
Symptomatic COVID-19, no signs of severity	No treatment	If risk factors*: Hcq + Lpv/r If no risk factors: no treatment	Consider Rdv (trials) Consider Hcq (trials) Consider Fpv (trials)
Symptomatic COVID-19, signs of severity (no ARDS)	Lpv/r or Hcq	Hcq + Lpv/r If initial RI: consider corticosteroids, Toc	Consider Rdv (trials) Consider Hcq (trials) Consider Fpv (trials) Consider Toc (trials) Consider Sar (trials)
Symptomatic COVID-19, ARDS	If PCR-pos: Rdv (1st choice) Lpv/r or Hcq (2nd choice) If PCR-neg: corticoids	Hcq + Rdv (1st choice) or Lpv/r (2nd choice) Consider corticoids, Toc	Consider Rdv (trials) Consider Hcq (trials) Consider Sar (trials) If Sar is not available, consider risks/benefits of Toc

RI = respiratory insufficiency; Fpv = favipiravir; Hcq = hydroxychloroquine, Lpv/r = lopinavir/ritonavir; Rdv = remdesivir; Sar = sarilumab; Toc = tocilizumab.

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