# 18th WHO Regulatory Update on COVID-19

**18 September 2020**

World Health Organization

## Key Messages

Global solidarity and leadership is the need of the hour. To stop the pandemic quickly and efficiently the world needs to resist “vaccine nationalism”—the desire of countries to go it alone. That approach will not end the crisis but perpetuate it.

## Highlights and main issues

- The inaugural meeting of the ACT Accelerator Facilitation Council was held on 10 September. The role of the Council is to facilitate the work of the ACT-Accelerator through political leadership and advocacy for collective solutions in the global interest, and for the mobilization of additional resources.
- Interim WHO guidance on antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays has been published. WHO has received three EUL submissions for antigen detection RDTs. All three products are undergoing EUL screening and review, the assessment outcomes will be shared as soon as available.
- WHO has published new guidance on corticosteroids for treating COVID-19 patients**.**
- WHO are actively engaging manufacturers for inclusion in the next stage of the Solidarity trial the use of anti-inflammatory drugs in hospitalized moderate to severely ill patients, as well as monoclonal antibodies for treatment.
- A WHO workshop resulted in a clear understanding of the vaccine safety ecosystem, globally, in terms of who is doing what. Regulators have a major role to play but they need to be well connected with immunization programmes in order to help monitor and interpret data on vaccine safety.
- A new tool has been launched to track and visualize clinical trials of COVID-19 vaccines.
- Experimental parameters that need to be controlled were discussed in a meeting of the WHO Animal Models group that discussed “What can animal models contribute to an understanding of vaccine enhanced disease?”
- With the resurgence of COVID-19 in several major cities, including Europe and the Americas, it is anticipated that there will be renewed shortages of ICU medicines. However, it is also anticipated that these shortages are unlikely to be as severe as those which occurred after the initial onset of the pandemic.

## Contents



## Promoting access to Medical Technologies and Innovation

The Access to COVID-19 Tools Accelerator (ACT-Accelerator) is a global collaboration to accelerate the development, production and equitable access to COVID-19 diagnostics, therapeutics and vaccines. It brings together leaders of government, global health organizations civil society groups, businesses and philanthropies to form a plan for an equitable response to the COVID-19 pandemic.

There are four pillars: diagnostics, therapeutics, vaccines and strengthening health systems.

- The **diagnostics pillar** aims to bring to the market high-quality rapid tests, train 10 000 healthcare professionals across 50 countries and establish testing for 500 M people in low- and middle-income countries. WHO is collaborating with FIND and The Global Fund on this pillar.
- The **therapeutics pillar** focuses on the manufacture and distribution of 250 M treatment for people suffering from COVID-19. WHO is collaborating with Unitaid and Wellcome Trust on this pillar.
- The **vaccines pillar** (Also called 'COVAX') works to maximize the development, equitable access and fair allocation across all countries. It aims to deliver 2 billion doses globally for high-risk populations, including 1 billion which will be purchased for low- and middle-income countries. WHO is collaborating with CEPI and Gavi on this pillar.
- The **health systems strengthening pillar** will support and enhance healthcare systems and local community networks needed to defeat this pandemic and ensure the world is

ready to take on the next one. WHO is collaborating with the World Bank and Global Fund on this pillar.

The ACT-Accelerator is already delivering substantial returns; over 170 countries are engaged in the new COVID-19 Vaccine Facility and ten candidate vaccines are under evaluation, 9 of them in clinical trials, giving the largest and most diverse COVID-19 vaccine portfolio in the world.

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## *In vitro* diagnostics

### Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays – interim WHO guidance

Since the beginning of the COVID-19 pandemic, laboratories have been using nucleic acid amplification tests (NAATs), such as real time reverse transcription polymerase chain reaction (rRT-PCR) assays, to detect SARS-CoV-2, the virus that causes the disease. In many countries, access to this form of testing has been challenging. The search is on to develop reliable but less expensive and faster diagnostic tests that detect antigens specific for SARS-CoV-2 infection. Antigen-detection diagnostic tests are designed to directly detect SARS- CoV-2 proteins produced by replicating virus in respiratory secretions and have been developed as both laboratory-based tests, and for near-patient use, so- called rapid diagnostic tests, or RDTs. The diagnostic development landscape is dynamic, with nearly a hundred companies developing or manufacturing rapid tests for SARS-CoV-2 antigen detection. Guidance on the use of Ag-RDTs will be regularly updated as new evidence becomes available. The Guidance is available at: https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays

### WHO EUL for SARS-CoV-2 virus IVDs

The WHO Prequalification Unit is assessing products for Emergency Use Listing (EUL) for candidate in vitro diagnostics (IVDs) to detect SARS-CoV-2. The following IVDs are eligible for EUL submission:

- Assays for the detection of SARS-CoV-2 nucleic acid;
- Rapid diagnostic tests and enzyme immunoassays for the detection of IgM/IgG to SARS-CoV-2; and
- Rapid diagnostic tests for the detection of SARS-CoV-2 antigens.

Manufacturers interested in the EUL submission are invited to contact WHO at diagnostics@who.int and schedule a pre-submission call.

**WHO EUL submissions and listing update**

Applicants submit their applications for assessment based on WHO instructions and requirements for NAT and Ag detection RDTs and IVDs detecting antibodies to SARS-CoV-2 virus submissions. 53 expressions of interest for NAT assays, 27 for antibody detection assays and 5 for antigen detection RDTs have been received so far. The status of each application is presented here. 20 products have been listed as eligible for WHO procurement based on their compliance with WHO EUL requirements:

| Date Listed | Product name | Product code(s) | Manufacturer |
|---|---|---|---|
| 03 April 2020 | cobas SARS-CoV-2 Qualitative assay for use on the cobas 6800/8800 Systems | 09175431190 and 09175440190 | Roche Molecular Systems, Inc. |
| 07 April 2020 | Primerdesign Ltd COVID-19 genesig Real-Time PCR assay | Z-Path-COVID-19-CE | Primerdesign Ltd. |
| 09 April 2020 | Abbott Realtime SARS-CoV-2 | 09N77-090 and 09N77-080 | Abbott Molecular Inc. |
| 24 April 2020 | PerkinElmer® SARS-CoV-2 Real-time RT-PCR Assay | SY580 | SYM-BIO LiveScience Co., Ltd |
| 07 May 2020 | Real-time fluorescent RT-PCR kit for detecting 2019-nCoV | MFG030010 | BGI Europe A/S |
| 14 May 2020 | Detection Kit for 2019 Novel Coronavirus (2019-nCoV) RNA (PCR- Fluorescence Probing) | DA0930, DA0931 and DA0932 | Da An Gene Co., Ltd. Of Sun Yat-sen University |
| 22 May 2020 | Novel Coronavirus (SARS-CoV-2) Real Time Multiplex RT-PCR Kit | RR-0485-02 | Shanghai ZJ Bio-Tech Co., Ltd |
| 22 May 2020 | FTD SARS-CoV-2 | 11416300 | Fast Track Diagnostics Luxembourg S.à.r.l. |
| 22 May 2020 | Multiple Real-Time PCR Kit for Detection of 2019-CoV | CT8233-48T | Beijing Applied Biological Technologies Co., Ltd. |
| 5 June 2020 | SARS-CoV-2 Nucleic Acid Test (Real-time PCR) | KH-G-M-574-48 | Shanghai Kehua Bio-engineering Co., Ltd |
| 11 June 2020 | Novel Coronavirus 2019-nCoV Nucleic Acid Detection Kit (Real Time PCR) | GZ-D2RM25 | Shanghai GeneoDx Biotechnology Co., Ltd |
| 15 June 2020 | COVID-19 Real-Time PCR Kit | HBRT-COVID-19 | Chaozhaou Hybribio Biochemistry Ltd. |
| 23 June | Xpert® Xpress SARS-CoV-2 | XPRSARS-COV2-10 | Cepheid AB |

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| 2020 | | | |
| 6 July 2020 | Simplexa COVID-19 Direct and Simplexa COVID-19 Positive control Pack | MOL4150, MOL4160 | DiaSorin |
| 9 July 2020 | COVID-19 Coronavirus Real Time PCR Kit | JC10223-1NW-50T | Jiangsu Bioperfectus Technologies Co.,Ltd |
| 14 August 2020 | TaqPath™ COVID-19 CE-IVD RT-PCR Kit | A48067 | Thermo Fisher Scientific |
| 14 August 2020 | Wantai SARS-CoV-2 RT-PCR | WS-1248 | Beijing Wantai Biological Pharmacy Enterprise Co.,Ltd |
| 28 August 2020 | SARS-CoV-2 Virus Detection Diagnostic Kit (RT-qPCR Method) | XC25073 | Ningbo Health Gene Technologies Co., Ltd. |
| 02 September 2020 | Novel Coronavirus (2019-nCoV) RT-PCR Detection Kit (commercial name: Fosun 2019-nCoV qPCR) | PCSYHF | Shanghai Fosun Long March Medical Science Co., Ltd. |
| 15 September 2020 | SARS-CoV-2 Nucleic acid detection kit based on Real-Time PCR platform | PGA4102P1 (liquid) / PGA4102P2 (lyophilized form) | Tellgen Corporation |

Since the last RPQ update the following products have been listed under the WHO EUL procedure:

1. The **SARS-CoV-2 Virus Detection Diagnostic Kit (RT-qPCR Method)** manufactured by **Ningbo Health Gene Technologies Co., Ltd**. is intended for in vitro qualitative detection of SARS-CoV-2 ORF1ab gene, N gene and S gene in specimens of sputum, nasopharyngeal or oropharyngeal swabs. Nucleic acid extraction should be performed using either bead-based nucleic acid extraction method such as the TANBead® extract system (Taiwan Advanced Nanotech, PN SLA32/ Maelstrom 9600) with a TANBead Viral Auto Plate kit (Taiwan Advanced Nanotech, PN 665A46), or spin column-based nucleic acid extraction method such as the RNeasy Mini Kit (Qiagen, PN 74104), following the manufacturer's instructions for the extraction procedure, respectively. The assay is intended to be used in combination with the Applied Biosystems® 7500/7500 Fast real-time PCR systems.
2. The **Novel Coronavirus (2019-nCoV) RT-PCR Detection Kit (commercial name: Fosun 2019-nCoV qPCR)** manufactured by **Shanghai Fosun Long March Medical Science Co., Ltd**. is a qualitative, manual real-time RT-PCR test intended for the qualitative detection of ORF1ab, E and N genes of nucleic acids from SARS-CoV-2 in oropharyngeal swab (throat swab) and sputum specimens from patients with signs and symptoms suggestive of COVID-19. The assay is intended to be used in combination with the QIAamp® Viral RNA Mini Kit (cat. #52904 or 52906),

the Fosun Nucleic Acid Extraction and Purification kit (cat. #PCSYMF), matching the automated TANBead® extraction system or the Genolution® NX-48 Viral RNA Kit (cat. #VN), matching the automated Genolution® NX-48 nextractor and the Applied Biosystems® 7500 intrument (software version 1.4 or 1.5), Roche LightCycler® 480 instrument (software version 1.5) or the SLAN-96P instrument (software version 8.2).

3. The **SARS-CoV-2 Nucleic acid detection kit based on Real-Time PCR platform** manufactured by **Tellgen Corporation** is intended for the in vitro qualitative determination of N gene and S gene for SARS-CoV-2 in human nasopharyngeal swab, oropharyngeal swab and sputum. The assay is intended to eb used with the Tellgen Nucleic Acid Extraction Kit (Cat.No. PF03X094), ThermoFisher (invitrogen) PureLink™ Viral RNA/DNA Mini Kit(Cat.No.12280050) or the ThermoFisher (Qiagen) QIAamp® Viral RNA Mini Kit (Cat.No.52904), and on of the instruments among the Roche LightCycler® 480 Real-time PCR System, Life Technology ABI7500 Real-Time PCR System, Hongshi SLAN®-48P Real-Time PCR System or SLAN®-96S Real-Time PCR System.

### Antigen detection RDTs

WHO has received three EUL submissions for antigen detection RDTs: the ***Panbio COVID-19 Ag Rapid Test Device (Nasopharyngeal)*** manufactured by Abbott Rapid Diagnostics Jena GmbH, the ***STANDARD Q COVID-19 Ag Test*** manufactured by SD Biosensor, Inc. and the **ESPLINE SARS-CoV-2** manufactured by Fujirebio, Inc. All three products are undergoing EUL screening and review, the assessment outcomes will be shared as soon as available.

### COVID-19 in vitro diagnostics listed by National Regulatory Authorities in IMDRF jurisdictions

To help countries, WHO publishes links to emergency lists, together with contact details, on IVDs authorized for use in the International Medical Device Regulators Forum (IMDRF) jurisdictions along with other useful information on policies and guidance. This information is updated on a weekly basis. The most recent update was published here.

**Note: WHO does not endorse any of the lists provided by NRAs. The information is provided exclusively to assist stakeholders with identifying the links to the various lists.**

## Therapeutics

### Corticosteroids for treating COVID-19 patients

WHO has published new guidance on corticosteroids for treating COVID-19 patients**.** WHO partnered with investigators of seven trials on corticosteroids to conduct a prospective meta-analysis of randomized trials for corticosteroid therapy for COVID-19 in order to rapidly provide additional evidence to build on RECOVERY data and inform guidance development. Drawing on these data, an international panel of content experts, patients, clinicians and methodologists produced recommendations following standards for trustworthy guideline development using the GRADE approach. The guidance considers an individual patient perspective and contextual factors (i.e. resources, feasibility, acceptability, equity) for countries and health care systems, and is available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1

### Update from the WHO Solidarity trial

Solidarity is the second-largest clinical trial in the world, with 24 countries doing active enrolment, and over 9000 patients recruited in 400 hospitals. It is also the largest trial of Remdesivir with 3000 randomized patients and will hopefully provide a definitive answer on the impact of Remdesivir on mortality and clinical progression.

WHO are actively engaging manufacturers for inclusion in the next stage of the trial the use of anti-inflammatory drugs in hospitalized moderate to severely ill patients, as well as monoclonal antibodies for treatment. In the coming weeks, data from the ongoing studies will be ready for dissemination and WHO will announce what the next stage of the Solidarity therapeutics trial will include.

### Research mapping of candidate therapeutics

A living research mapping of candidate COVID-19 therapeutics, displaying studies per country, showing study design, disease severity in study participants, and type of treatment being studied, as well as network maps of these studies, has been made available at: https://www.covid-nma.com/dataviz/

### Living synthesis of Covid-19 study results

A list of treatment comparisons, a summary of the evidence for that comparison, and a detailed description of primary studies, including a risk of bias assessment is at:

https://covid-nma.com/living_data/index.php

## Vaccines

### COVAX, the ACT-accelerator vaccines pillar, and the COVAX Facility

Phase III trials for some vaccine candidates began in July 2020. It is expected that the results from this large-scale trial phase (enrolling at times 30 000-60 000 people) will begin to come in at the end of the year. After the data is available, regulatory authorities will need to assess the safety and efficacy, and manufacturing for approved vaccines will begin. Given this timeline, it is expected that doses will begin arriving in countries in the middle of 2021 (second or third quarter). As these first doses will be limited, there is a need to prioritize them for vulnerable groups like health workers and older people. WHO is developing a **global allocation framework,** for vaccines and other COVID-19 tools**,** based on fair and equitable access principles to facilitate equitable distribution.

### Vaccine safety ecosystem

WHO held a vaccine safety ecosystem workshop on September 9th. The objectives of the workshop were to review the challenges in addressing the end-to-end safety of COVID-19 vaccines, to map current international efforts in addressing those challenges, to identify overlaps, gaps and potential synergies, and agree on a way forward.

The workshop resulted in a clear understanding of the vaccine safety ecosystem in terms of who is doing what. It is clear that regulators have a major role to play and that they need to be

well connected with immunization programmes in order to help interpret data on vaccine safety. In some countries this is already the case; in many it is not. So, a key outcome from the workshop is the need for a plan to connect the dots, which is something that WHO will do as a follow-up to the workshop and provide a practical plan of action to enable the required connections to happen.

Another key message was that in many countries, immunization programmes are not geared up to deliver immunizations to health-care workers and the elderly, key target groups for COVID-19 vaccines. This has implications for vaccine safety since background rates of AEFIs will not be known in many countries for these populations.

## WHO standards for DNA vaccines

The text has been published of "Guidelines for assuring the quality, safety, and efficacy of plasmid DNA vaccines" adopted by the Seventy-first Meeting of the World Health Organization Expert Committee on Biological Standardization, 24–28August 2020. A definitive version of this document, which will differ from the post-ECBS version in editorial but not scientific details, will be published in the WHO Technical Report Series. The guideline is available at: https://www.who.int/publications/m/item/DNA-post-ECBS-1-sept-2020)

## Living mapping and living systematic review of Covid-19 studies

A new tool has been launched to track and visualize clinical trials of COVID-19 vaccines. This builds on the existing work to map and review candidate therapeutics. A strict process to identify, appraise and synthesize study results is used to construct a **living mapping of ongoing research** to monitor in real-time any new evidence that becomes available for treating and preventing Covid-19. In this way, gaps and deficiencies of existing evidence can be identified early enough and to help prioritize and optimize future research. Through the process of **living systematic reviews**, all the available evidence addressing specific clinical outcomes related to Covid-19 are continuously collected and critically appraised. Then, using **network meta-analysis**, the available study results are synthesized and compared simultaneously with all possible interventions that could be used in the same clinical setting. This work receives some funding from the Agence Nationale de la Recherche (ANR), the World Health Organization (WHO), Cochrane France, Center of Research in Epidemiology and StatisticS (CRESS), Centre d'Epidémiologie Clinique (GHU Cochin, Hôtel Dieu, Assistance Publique Hôpitaux de Paris (APHP) and Université de Paris) and the Federal Ministry of Health, Germany. The tool is available at: https://covid-nma.com/vaccines/mapping/

## Landscape of candidate vaccines for SARS-CoV-2

A landscape analysis of candidate SARS-CoV-2 vaccines is regularly published by WHO. Currently, over 180 vaccines are at some stage of development. Of these, **36 vaccine candidates are in human trial**. About 9 are in or entering phase III trials. There are several others currently in phase I/II, which will enter phase III in the coming 2 months. This is a very robust pipeline – the more candidates, the more opportunities for success (typically success rate of candidate vaccines is 10%). The candidate vaccines are of various types – virus vaccines using live attenuated virus, viral vector vaccines, protein-based vaccines, and nucleic acid or RNA and DNA vaccines, which are completely new platforms.
The landscape is available at:

https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
(17 September 2020)

## Convalescent plasma

In response to the issue of an Emergency Use Authorization of COVID-19 Convalescent Plasma (CCP) by US FDA, WHO convened a teleconference on 9 September 2020, attended by WHO Regional Advisors, US FDA, EU, ECDC, the WHO Blood Regulator Network (BRN), Expert Advisory Panel on Blood Transfusion Medicine and ECBS Blood and IVD Track Member. The purpose of the TC was to share information relevant to policy making on collection and use of CCP to consider implications for WHO guidance.

The US FDA shared data that supported their decision to issue an EUA. The data supported the conclusion that it is reasonable to believe that COVID-19 Convalescent Plasma may be effective in the treatment of some patients with COVID-19 and known and potential benefits of CCP outweigh the known and potential risks. Clinical benefit is most likely to be seen in patients treated early in disease course, and treated with higher titer CCP. However, quantitative assays for SARS-CoV-2 neutralizing antibodies remain limited and randomized controlled trials (RCTs) are needed to show definitive evidence of safety and efficacy, and also to determine the optimal product attributes and appropriate patient populations.

RCTs are ongoing in a number of countries (e.g. UK, Germany, France) while single-armed studies, case-control studies and monitored use protocols are proceeding in parallel. The EU has a Europe-wide database of the assessed use/trials of CCP to support high quality evaluation of COVID-19 Convalescent Plasma throughout Europe.

The WHO ECBS has endorsed development of WHO International Standard (IS) for anti-SARS-CoV-2 antibody. The candidate IS is being investigated as a standard for neutralizing as well as binding activity. The ECBS expressed a strong view that CCP should be calibrated in International Units as soon as the antibody standard became available. Access to laboratory testing for neutralizing antibodies is an issue in many low- and middle-income countries. The possibility of centralized testing of neutralizing antibody levels to support obtaining quality data for analysis and possible pooling of study outcomes was discussed.

Finally, the meeting concluded that the WHO interim guidance
https://www.who.int/publications/i/item/maintaining-a-safe-and-adequate-blood-supply-during-the-pandemic-outbreak-of-coronavirus-disease-(covid-19)
remains valid and be further reviewed when new data from ongoing clinical trials become available.

## Research protocols, assays and reference standards

### WHO Working Group on Assays and Reference Preparations

A centralized laboratory network for measurement of immune responses elicited by SARS-CoV-2 vaccines was described at the 16 September meeting. Currently there are more than 300 COVID-19 vaccine developers worldwide which means that technology differences, biological variation, and assay differences make comparison of results between studies difficult. To resolve some of these problems, CEPI has created a centralized laboratory network. So far 4

laboratories are in the network, and 3 more will join soon. This network is open to all COVAX funded and non-funded vaccine developers with the aim to test samples from pre-clinical to phase 2 clinical trials, to support SARS-CoV-2 vaccine developers on the pathway towards licensure and increase the chances of finding a successful vaccine. Efforts have been made to select high quality laboratories and the most advanced assays, and to harmonize protocols and key reagents. Currently ELISA, pseudoviral neutralization, wild type virus neutralization and ELISPOT are available in the network and relevant key reagents are provided to the laboratories in the network along with a coordinated process for assay set-up and validation.

A summary of a SARS-CoV-2 Neutralizing assay Concordance Survey (SNACS) was also presented. A panel of 21 samples were provided to the participating labs. 48 labs reported data from various assays including live virus neutralization assay and pseudovirus (PsV) neutralization assay. Preliminary analysis found there are many variables that need to be considered in the complex dataset analysis including: laboratory experience, assay types, reagents, readouts, cells used and backbone vectors. Preliminary conclusions are:

- Using a common SOP largely improved the concordance among labs.
- There was a 2 -log difference in ID50 titers and 1-log difference in ID80 titers across live virus and PsV neutralization assays.

An update was provided to the group on a study to evaluate a candidate WHO International Standard (IS) for SARS-CoV2 antibodies and a companion reference panel. The study involves 50 laboratories from 14 countries, contributing data from 67 ELISAs, 16 live virus neutralization assays, 15 PsV based neutralization assays and some other methods. The organiser, NIBSC, UK, a WHO collaborating Center, is currently receiving data/reports from participating laboratories. A report of the study should be available for public consultation by November 2020 and, if found fit for purpose, for establishment as a WHO IS in December 2020.

**WHO Working Group on Animal Models**

"Should challenge stocks for animal model studies be standardized?" was discussed by a panel in the 3 September meeting. For many research studies completed so far standardized challenge stocks have not been used and there is a reassuring agreement in overarching conclusions. Best practices were considered more important than standardized stocks for research studies. It was also noted that variation in animal experiments may be due to variations in the challenge virus, or variations in the animals and their husbandry, or all of these factors. Therefore, it is best practice to include control groups in all experiments and not to rely, for example, on historical controls. Nevertheless, the use of a well-characterized challenge stock would enable drift due to animal factors to be quickly recognized if predicted results in experiments were not obtained. One discussant commented that standardized stocks were not required for regulatory decision making on individual products. However, from a public health perspective where the performance of several vaccines or therapies are being compared in animal models then standardized challenge virus stocks are a necessity, so that this potential source of variation is adequately controlled. Finally, it was noted that production of large volumes of standardized stock is technically challenging and WHO were encouraged to complete their ongoing work to document factors that minimize heterogeneity during large-scale virus cultivation.

"What can animal models contribute to an understanding of vaccine enhanced disease" was debated by a panel in the 17 September meeting. There was an agreement that

immunization/challenge studies on this topic need careful design since a number of confounders have been identified that may lead to misleading conclusions. For example, enhancement can be triggered by an immune response to cellular proteins present as contaminants in the vaccine or challenge virus stock. The dose of vaccine, and timing of the challenge after immunization are other important variables. Breakthrough infections are needed to evaluate if enhanced disease occurs so titration to establish a suitable vaccine dose to enable this to happen was recommended. Timing of the challenge to a time when immunity is waning is also necessary. From a regulatory perspective, the animal experiments need to be sufficiently controlled for these variables so that the results are actionable. It was also noted that data from animal models may not necessarily be predictive for humans, so good quality human clinical trial data are always essential. Parameters that are being evaluated in humans include the Th1/Th2 balance of the immune response, although there is no accepted ratio as yet, and the balance of neutralizing to non-neutralizing antibodies, but here too there is, as yet, no accepted ratio.

## Supply Chain

### Shortages:

With the resurgence of COVID-19 in several major cities, including Europe and the Americas, it is anticipated that there will be renewed shortages of ICU medicines. However, it is also anticipated that these shortages are unlikely to be as severe as those which occurred after the initial onset of the pandemic.

This less severe prediction is based on two factors. First, some countries have developed stockpiles or reserve inventories in anticipation of a potential resurgence. There are no international mechanisms to report on the content or quantities included in national stockpiles. While the information is important, it difficult to obtain, partly because some inventories are strategic or privately held and partly because some are inventories of API that were secured for the purposes of pharmacy-level compounding of certain medicines.

A second factor in the prediction of less severe shortages is that improved treatment guidance and access to testing have reduced the number of patients that require hospitalization, including extended intensive care stays, in many countries.

With concerns about the resurgence in India and the impact on manufacturing, local industry associations presently report no shortages of medicines from their manufacturing base. In addition, a national guideline regarding ventilation and air conditioning in factories has been distributed to improve safety conditions for staff in pharmaceutical factories.

Monitoring the availability of malaria medicines and diagnostics shows a persistent shortage of malaria diagnostics, artemether-lumafantrine, and injectable artemisinin-based therapies. The shortages have numerous root causes, including demand for repurposed medicines, competition for production capacity for diagnostics, poor uptake of treatment in certain zones and other causes. Discussions with manufacturers continue to show positive activity towards a more stable supply.

WHO and partners have secured an inventory of dexamethasone, which will be allocated and distributed by UN partners to countries that are dependent on international procurement assistance. It is noted that this inventory is limited and would be insufficient to cover all unmet needs.

WHO is developing an application that uses machine learning to monitor active shortage information in several markets and will be making it available in 2021.

**Watch list and active shortages:**

In addition to the above, WHO is still maintaining a watch list on the following products. There are not active reports of shortages, but the watch list remains in force:

- Antibiotics: azithromycin, levofloxacin, metronidazole, amoxiclav, piperacillin, tazobactam
- epinephrine and norepinephrine
- Benzodiazepine sedatives: midazolam and lorazepam
- Nonbenzodiazepine sedatives: propofol
- Antipsychotics: haloperidol
- Neuromuscular relaxants: succinylcholine, atracurium, or vecuronium.
- Opioids: morphine and fentanyl
- Malaria treatments: hydroxychloroquine, chloroquine, artemether-lumafantrine, artemisinin-based combination therapies, sulfadoxine-pyrimethamine + amodiaquine)
- NCD: Metformin and insulin
- Antipyretics: paracetamol (aka acetaminophen)
- PPE
- Oxygen and related equipment
- Ventilators

The following medicines remain in shortage, with WHO working with suppliers on potential solutions:

- HIV: Lopinavir/ritonavir
- Experimental medicines: remdesivir
- Corticosteroids: salbutamol (aka albuterol) inhalers, dexamethasone

## Medical Devices

Specifications for medical devices have been released to support national procurement, especially to facilitate reviews of offers and products. Without an established standard for performance, or at least a complete technical specification, there have been increased risks for the procurement of devices, equipment and other consumable products that are not sufficiently suitable for their purpose. Please see the WHO Medical Devices page on: www.who.int/medical_devices/priority/COVID-19/en/