Regulation of in vitro diagnostics, therapeutics, and vaccines
WHO Update – 13
Coronavirus disease 2019 (COVID-19)
03 July 2020

World Health Organization

Please do not quote or publish: this update is for internal WHO purposes and for disseminating information to specific stakeholders

Key Messages

Regulators should use regulatory agility as much as possible to ensure both rigour and speed so that clinical trials remain compliant with Good Clinical Practice, on track to produce reliable results as quickly as possible while protecting the rights and safety of the participants.

Highlights and main issues

- The WHO Research Forum, 1-2 July, agreed on the need for more trials to test antivirals, immunomodulatory drugs and anti-thrombotic agents, as well as combination therapies, at different stages of the disease.
- Data presented in the Forum showed that most internationally funded research projects have so far favoured high-income countries, with very few funded in low- and middle-income countries, highlighting the importance of the ACT-Accelerator Initiative to speed up the development and equitable deployment of COVID-19 tools.
- An independent review also reported in the Forum that whilst there are about 1 700 registered clinical trials for therapeutics, many did not begin or have only enrolled a few patients. The three major trials contributing to evidence on hydroxychloroquine, lopinavir/ritonavir and steroids including dexamethasone were the RECOVERY Trials from UK, ACTIV Trials from the US, and the WHO Solidarity Trial.
- Preliminary data on lopinavir/ritonavir reported in the Forum suggests a lack of an effect, but analysis is ongoing.
- There are currently 17 vaccines in clinical trial; all are in randomized controlled trials. WHO expects more to follow as there are around 150 candidate vaccines in total.
- The WHO EUL scope for IVDs has been expanded to antibody detection enzyme immunoassays.

Virtual Global Research and Innovation Forum on COVID-19

The World Health Organization held a two half-day virtual summit on 1st and 2nd July, to take stock of the evolving science on COVID-19 and examine progress made so far in developing effective health tools to improve the global response to the pandemic.

The event brought together researchers, developers and funders from all over the world, all of whom shared

approaches and raw data freely, in a show of solidarity from the global science community. All major research institutes carrying out trials shared their data with a view to speeding up scientific discovery and implementation of solutions.

The group reviewed the latest data from the WHO Solidarity Trial and other completed and ongoing trials for potential therapeutics: hydroxychloroquine, lopinavir/ritonavir, remdesivir and dexamethasone. They agreed on the need for more trials to test antivirals, immunomodulatory drugs and anti-thrombotic agents, as well as combination therapies, at different stages of the disease.

The meeting heard an analysis of 15 vaccine trial designs from different developers, and discussed criteria for conducting robust trials to assess safety and efficacy of vaccine candidates. Participants discussed the use of a global, multi country, adaptive trial design, with a common data safety monitoring board, and clear criteria to advance candidates through the various stages of trials.

They noted that most internationally funded research projects have so far favoured high-income countries, with very few funded in low- and middle-income countries, highlighting the importance of the Access to COVID-19 Tools Accelerator (ACT-Accelerator) Initiative to speed up the development and equitable deployment of COVID-19 tools.

More evidence is emerging that transmission from humans to animals is occurring, namely to felines (including tigers), dogs and minks.

The Summit hosted over 1 000 researchers and scientists from all over the world and addressed the following topics:

- virus: natural history, transmission and diagnostics;
- animal and environmental research on the virus origin, and management measures at the human-animal interface;
- epidemiological studies;
- clinical characterization and management;
- infection prevention and control, including health care workers' protection;
- candidate therapeutics R&D;
- candidate vaccines R&D;
- ethical considerations for research and;
- integrating social sciences in the outbreak response.

Link: WHO media briefing on 2nd Global COVID-19 R&D Forum

Act-Accelerator update

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 the 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 was launched at the end of April 2020 by the Director General of the World Health Organization, the President of France, the President of the European Commission, and The Bill & Melinda Gates Foundation. It presented its investment case on 26 June 2020. The consolidated investment case calls for US$ 31.3 billion over the next 12 months. US$ 3.4 billion has been contributed to date, resulting in a funding gap of US$ 27.9 billion, of which US$ 13.7 billion is urgently needed.

Link: The Access to COVID-19 Tools (ATC) Accelerator

Alignment of approaches by regulatory groups

Global regulators discuss data requirements for phase 3 trials of COVID-19 vaccines

Under the umbrella of the International Coalition of Medicines Regulatory Authorities (ICMRA), international regulators discussed COVID-19 vaccine development and the necessary evidence required for regulatory decision-making at the second regulatory workshop on COVID-19 vaccines. The meeting was jointly organised by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) on 22 June 2020. The workshop brought together 100 participants from more than 20 countries, representing 28 medicines regulatory authorities and the World Health Organization.

Many researchers around the world are currently working on vaccines against COVID-19 but a rapid authorisation of COVID-19 vaccines will only be possible if robust and sound scientific evidence on vaccine candidates' quality, safety and efficacy is generated. International convergence of data requirements is intended to encourage and accelerate the development of vaccines as a global public health good.

During the workshop, global regulators focused on requirements for non-clinical and clinical data from early phase studies that are needed before proceeding with advanced (phase 3) clinical trials with COVID-19 vaccine candidates in humans. They exchanged views on key aspects, such as eligibility criteria for inclusion of diverse populations, primary endpoints and other methodological considerations related to the design of phase 3 clinical trials.

Meeting participants agreed that regulatory convergence, to the extent possible, on certain key aspects of phase 3 clinical trial designs will help developers to generate robust evidence on the quality, safety and efficacy of potential COVID-19 vaccines that meets the needs of regulators around the globe. This is critical for expediting and streamlining global development and authorisation of vaccines against COVID-19.

More details on the discussions and the outcomes of the meeting will be available in the next Regulatory Update.

ICMRA statement on clinical trials

ICMRA members have stepped up their global collaboration to facilitate and expedite the development and evaluation of diagnostics and therapeutics, including possible vaccines, against SARS-CoV-2. Regulators have worked to anticipate issues that make clinical trials challenging to conduct during a pandemic and have used regulatory agility as much as possible to address these needs. The aim to ensure both rigour and speed

so that trials remain compliant with Good Clinical Practice, on track to produce reliable results while protecting the rights and safety of the participants. Regulators are committed to supporting investigators and healthcare professionals so that participants can continue to be enrolled in priority trials that will provide the robust and reliable results needed to support regulatory decisions.

ICMRA Statement on Clinical Trials (24 June 2020)

In vitro diagnostics

WHO EUL for SARS-CoV-2 virus IVDs: scope expanded to antibody detections enzyme immunoassays

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

On 3 July 2020 the EUL scope will be expanded to antibody detection enzyme immunoassays. The following IVDs are therefore eligible for EUL submission:

- Assays for the detection of SARS-CoV-2 nucleic acid;
- Rapid diagnostic tests 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 are asked to 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[1].

47 expressions of interest for NAT assays, 12 for antibody detection RDTs have been received so far.

The status of each application: update (30 June 2020)

13 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
23 June 2020	Xpert® Xpress SARS-CoV-2	XPRSARS-COV2-10	Cepheid AB
15 June 2020	COVID-19 Real-Time PCR Kit	HBRT-COVID-19	Chaozhaou Hybribio Biochemistry Ltd.
11 June 2020	Novel Coronavirus 2019-nCoV Nucleic Acid Detection Kit (Real Time PCR)	GZ-D2RM25	Shanghai GeneoDx Biotechnology 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
22 May 2020	Novel Coronavirus (SARS-CoV-2) Real Time Multiplex RT-PCR Kit	RR-0485-02	Shanghai ZJ Bio-Tech Co., Ltd
21 May 2020	FTD SARS-CoV-2	11416300	Fast Track Diagnostics Luxembourg S.à.r.l.

[1] The link to the instructions for submission of IVDs detecting antibodies to SARS-CoV-2 will be posted on the WHO website by 4 July 2020

19 May 2020	Multiple Real-Time PCR Kit for Detection of 2019-CoV	CT8233-48T	Beijing Applied Biological Technologies Co., Ltd.
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
07 May 2020	Real-time fluorescent RT-PCR kit for detecting 2019-nCoV	MFG030010	BGI Europe A/S
24 April 2020	PerkinElmer® SARS-CoV-2 Real-time RT-PCR Assay	SY580	SYM-BIO LiveScience Co., Ltd
09 April 2020	Abbott Realtime SARS-CoV-2	09N77-090 and 09N77-080	Abbott Molecular Inc.
07 April 2020	Primerdesign Ltd COVID-19 genesig Real-Time PCR assay	Z-Path-COVID-19-CE	Primerdesign Ltd.
03 April 2020	cobas SARS-CoV-2 Qualitative assay for use on the cobas 6800/8800 Systems	09175431190 and 09175440190	Roche Molecular Systems, Inc.

On 23 June 2020, WHO listed the following NAT assay under the emergency use listing procedure:

- The **Xpert® Xpress SARS-CoV-2** manufactured by **Cepheid AB** is a real-time RT-PCR test intended for the qualitative detection of nucleic acid from the SARS-CoV-2 in nasopharyngeal swab, nasal swab, or nasal wash/aspirate specimen collected from individuals who are suspected of COVID-19 infection. The Xpert Xpress SARS-CoV-2 test is performed on GeneXpert Instrument Systems. The GeneXpert Instrument Systems automate and integrate sample preparation, nucleic acid extraction and amplification, and detection of the target sequences in simple or complex samples using real-time PCR assays. The systems consist of an instrument, computer, and preloaded software for running tests and viewing the results. The systems require the use of single use disposable cartridges that hold the RT-PCR reagents and host the RT-PCR process. The Xpert Xpress SARS-CoV-2 test is intended to be performed by trained users in both laboratory and near patient testing settings.

IVDs at the core of the ACT Accelerator

Launched at the end of April 2020, the Access to COVID-19 Tools (ACT) Accelerator is organized into four pillars of work. The diagnostics pillar focuses on four areas of work which are critical for speeding up an end to the pandemic; R&D, market readiness, supply and country preparedness.

The WHO EUL assessments and support to in-country authorization or listing of IVDs for COVID-19 are at the core of WHO's support to market readiness and come to complement partners' efforts towards equal and adequate access to diagnostic tools. A diagnostics investment case was recently published to advocate for global solutions in defeating the virus.

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.

The most recent lists: update (29June 2020)

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

Updates on therapeutics reported at the WHO Global Research Forum, 1-2 July 2020

An independent review suggested that the RECOVERY Trials from UK, ACTIV Trials from the US, and the WHO Solidarity Trial had been contributing to build evidence on hydroxychloroquine, lopinavir/ritonavir and steroids including dexamethasone. Preliminary data from these three trials confirmed that hydroxychloroquine does not have any effect on reducing mortality. The preliminary data on lopinavir/ritonavir also suggests a lack of an effect, but analysis is ongoing. WHO will carry out a full systematic review on steroids and Remdesivir.

The independent review also found that whilst there are about 1 700 registered clinical trials for therapeutics, many did not begin or have only enrolled a few patients.

In contrast, as of 1 July, nearly 100 countries in all 6 WHO regions have joined or in the process of joining the SOLIDARITY trial. Thirty-nine countries have approvals, of which 21 have already actively recruited patients across 351 hospitals, involving over 1 200 clinical researchers. In all, nearly 5 500 hospitalized COVID-19 patients have been randomized.

Dexamethasone and COVID-19 – WHO actions

Dexamethasone is a corticosteroid used in a wide range of conditions for its anti-inflammatory and immunosuppressant effects. It was tested in hospitalized patients with COVID-19 in the United Kingdom's national clinical trial RECOVERY and was found to have benefits for critically ill patients. According to preliminary findings shared with WHO (and now available as a preprint), for patients on ventilators, the treatment was shown to reduce mortality by about one third, and for patients requiring only oxygen, mortality was cut by about one fifth. WHO is in the process of updating treatment guidelines to include dexamethasone or other steroids.

In response to the news of the clinical trial results, WHO has secured supply of Dexamethasone for distribution to low and middle income countries, mapped existing and potential manufacturers and is carefully monitoring supply chains for possible shortages.

To assist country offices and other stakeholders, WHO published a series of questions and answers on dexamethasone:

Q&A: Dexamethasone and COVID-19 (25 June 2020)

RECOVERY trial - Closure of lopinavir-ritonavir treatment arm

The UK RECOVERY trial has found that there is no beneficial effect of lopinavir-ritonavir in patients hospitalised with COVID-19. The investigators have therefore closed randomisation to that treatment arm. A total of 1 596 hospitalised patients were randomised to lopinavir-ritonavir and compared with 3 376 patients randomised to usual care alone. There was no significant difference in the primary endpoint of 28 - day mortality[2] and the results were consistent in different subgroups of patients. There was also no evidence of beneficial effects on the risk of progression to mechanical ventilation or length of hospital stay. The Medicines and Healthcare products regulatory Agency (MHRA) in the UK is working closely with researchers to ensure that the full results will be available as soon as possible.

[2] (22.1% lopinavir-ritonavir vs. 21.3% usual care; relative risk 1.04 [95% confidence interval 0.91-1.18]; p=0.58)

Remdesivir

Remdesivir is a direct-acting antiviral agent. It is one of the treatment options under study as part of the WHO Solidarity trial. Results from that trial will be available in the near future on possible efficacy of this drug. WHO is working on several fronts – through ACT-Accelerator and C-TAP – to ramp up production of promising COVID-19 health tools and ensure equitable access across all countries.

Research mapping of candidate therapeutics for COVID-19

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

Adverse drug reactions

The eighth analysis provides characteristics of the reports on WHO Solidarity trial drugs and drugs reported more than 100 times into VigiBase.

There were 486 new reports for hydroxychloroquine during this time period, adding to a cumulative total of 1 932 reports. Hydroxychloroquine was a single suspected drug in 224 cases. The adverse drug event pattern for hydroxychloroquine seems to follow previously weeks observations with electrocardiogram QT prolonged, hepatic related events and gastrointestinal ADRs such as vomiting, nausea, diarrhoea among the top reported ADRs during this period. These visualisations are presented for each of the drugs reviewed as in Figure 4.

During this reviewing period 40 new reports in which chloroquine was reported as suspecting or interacting drugs were reviewed. in which chloroquine was reported as suspecting or interacting drugs were reviewed. The 5 most frequently reported MedDRA Preferred Terms were: vomiting (13 reports), abdominal pain upper (11), nausea (7), diarrhoea (7), vertigo (6).

120 new reports in which lopinavir;ritonavir were reported during this reviewing period as suspecting or interacting drugs were reviewed. The most commonly reported ADRs continued to be those which are included on the product labelling for lopinavir;ritonavir.

Remdesivir is an antiviral substance against RNA viruses including SARS-CoV-2. There is a total of 404 reports of remdesivir in VigiBase. During this reviewing period, 328 new remdesivir reports were shared, of which in 315 the drug was reported as single suspected. The new reports in this review comprise 81% of the cumulative total of reports. In previous UMC COVID-19 reviews reporting of kidney and liver function disturbances and skin reactions were common for remdesivir.

A descriptive analysis of the new reports (01 July 2020)

Vaccines

Updates on vaccines reported at the WHO Global Research Forum, 1-2 July

There are currently 17 vaccines in clinical trials; all are in randomized controlled trials. WHO expects more to follow as there are some 150 candidate vaccines under development. There are 4 kinds of vaccine candidates in the pipeline: virus vaccines using inactivated or live attenuated virus, viral vector vaccines, nucleic acid based vaccines (DNA/RNA vaccines) and protein vaccines. This robust vaccine pipeline gives the scientific community hope, even if there many unpredictable factors which will determine their success.

The developers of 15 of the 17 vaccines in clinical trial presented their phase III designs at the Research Forum on 1st and 2nd July. The Forum allowed the international community to look at the different designs and compare them. All the developers were targeting critical populations and had proposed end points that are compatible with public health needs. There was an open and robust discussion of stringent success criteria for regulators to approve effective vaccines and for public health officials to make informed decisions on deployment of successful products.

FDA guidance on "Development and Licensure of Vaccines to Prevent COVID-19"

The U.S. Food and Drug Administration has published guidance with recommendations for those developing COVID-19 vaccines for the ultimate purpose of licensure. The guidance, which reflects advice the FDA has been providing over the past several months to companies, researchers, and others, describes the agency's current recommendations regarding the data needed to facilitate the manufacturing, clinical development, and approval of a COVID-19 vaccine. Key considerations to satisfy requirements for chemistry, manufacturing and control, nonclinical and clinical data through development and licensure, and for post-licensure safety evaluation, are described. The FDA expects that a COVID-19 vaccine would prevent disease or decrease its severity in at least 50% of people who are vaccinated.

Landscape of candidate vaccines for SARS-CoV-2

A landscape analysis of candidate SARS-CoV-2 vaccines is regularly published by WHO.

Landscape of COVID-19 candidate vaccines (02 July 2020)

Convalescent plasma

Guidance on maintaining a safe and adequate blood supply during COVID and on the collection of COVID-19 convalescent plasma

Updated interim guidance from WHO on the management of the blood supply in response to the pandemic outbreak of coronavirus disease including recommendations on collection of COVID-19 convalescent plasma has been published[3]. It is intended for blood services, national health authorities, and others responsible for the provision of blood and blood components and integration of the blood system within the public health system. WHO will continue to update this guidance as new information becomes available.

[3] Guidance will be posted on the WHO website by 7 July 2020

Enabling research: Animal models, clinical trial protocols, assay development, standards

WHO Working Group on Assays and Reference Preparations

The 24 June meeting discussed assay comparison studies and tools.

The University of Colorado, Centre for Global Health (CGH) described a COVID-19 serology control panel. There are 2 500 sets of the panel, which comprises positive, weak positive and negative samples. There are 5 dried tube specimens per panel. Samples in the panel are pooled convalescent plasma from multiple donors which have been tested by various neutralization assays. The samples in the panel have been tested head to head with other panels such as NIBSC panel. Anticipated uses include training; intra-laboratory validation of reagents; research studies that require common calibration; and head-to-head comparison of test kits. CGH is able to provide a service to analyze results, provide guidance and support, and troubleshooting. The timeline for availability of the control panel is mid-August 2020. Questions were asked whether there is any difference between testing plasma (the panel samples) and serum samples (obtained from vaccine clinical trials). In reply, the group were informed this issue will be investigated in the forthcoming collaborative study led by NIBSC to evaluate a candidate International Standard (IS) for SARS-CoV-2 antibody.

The US NIH/NIAID gave an update of a taskforce established to develop and standardize assays for COVID - 19 vaccine clinical trials. ELISA and microneutralization assays should be qualified by late July; pseudovirus-based neutralization assays (PsV-NA) are at the development stage using both HIV and lentivirus backbones. Discussions included the use the assays in pre-clinical studies, and the need to participate in the NIBSC collaborative study on the candidate WHO IS. WHO supported the idea of centralized laboratories performing ELISA, neutralization assay and PsV-NA to evaluate pre-clinical and clinical samples.

PATH gave an update of their work, with support from BMGF, to establish a bio-repository. The current focus is to serve as a global resource for the development and validation of in-vitro diagnostics for COVID - 19. PATH have obtained a large collection of clinical samples including nasal swabs, tongue swabs, serum, and plasma. The samples were PCR positive and are to be characterized by other assays.

Washington COVID-19 Biorepository

The group was also informed of a SARS-CoV-2 neutralizing assay concordance survey (EQAPOL SNACS project), which is intended as an initial survey of assay concordance across a large number of laboratories and assay types. The survey should help assess specificity, accuracy and precision of laboratories. The survey will provide baseline data for further concordance testing and design of a proficiency testing program for key laboratories involved in clinical trials.

Timelines:

- Send-out: July 15, 2020
- Data check-out: Aug 7, 2020
- Data analysis: Aug 8-14, 2020
- Report: Aug 15, 2020

WHO Working Group on Animal Models

The 25 June meeting heard of plans to make transgenic hACE2 mice commercially available, with distribution expected from autumn. Evaluation of a candidate vaccine, a VSV vector expressing the SARS - CoV-2 spike protein, in a golden Syrian hamster model was also reported.

The hamsters had moderate clinical signs (20% loss of body weight, and lethargy, measured by a novel night-sensitive movement methodology) and lung pathology when challenged by SARS-CoV-2.

Immunization protected the animals against virus challenge. A comparative study of the sensitivity of rhesus macaques, baboons and marmosets to SARS-CoV-2 was reported too. Baboons were found to be most sensitive in terms of clinical signs and lung pathology, followed by rhesus, with marmosets being least sensitive. Moreover, an age-related effect was seen with older baboons being most affected; this was not seen with the other species. The investigators concluded that baboons offered a promising model to test candidate therapeutics whilst rhesus macaques are a good model for evaluation of vaccines.

Supply chain updates from WHO HQ and Regional Offices

Shipments from UN partners

Shipments to countries continue from the UN supply chain consortium and the online portal is being used in an increasing number of countries.

Shortages

WHO recognizes the need to proactively seek information about shortages related to COVID-19 through its networks, considering the fast-changing environment where publicly available databases often capture after a shortage is already having negative impact.

Shortages for ICU products had somewhat normalized since the first wave of countries affected by COVD-19; however, the same pattern of shortages has re-emerged in South America, where cases are increasing. These shortages are related to rapid increases in demand where increased manufacturing will be necessary, but where the related time to produce will not resolve the short term problem. In the immediate term, managing available inventories, working with alternate suppliers have been the most productive solutions. The watch list below includes the medicines affected.

Shortages from speculative procurement have unfortunately increased, despite the urging from WHO and partners to engage in rational forecasting and planning.

For example, dexamethasone is broadly available for multiple indications. In relative terms, the percent increase due to severe COVID cases would not be large; however, spikes in orders to create stockpiles and the like are threatening equitable access to this product. Another problem with dexamethasone is that it was in moderate shortage prior to the increased demand from the clinical trials. The problem was related to delays in managing manufacturing variances in North America and Western Europe. Information from other markets, which are generally served by a different group of manufacturers remains pending.

The recent media information regarding monopolization of the supply of remdesivir is also a concern for WHO. The product is made under an open license by multiple suppliers and WHO is working with these sources.

Quality assurance in supply chain

National governments, local UN offices and civil society procurers who are purchasing PPEs, equipment and diagnostics from some national markets have reported challenges with local capacity to perform sufficient quality assurance reviews of the products. The concern is regarding products that have not been reviewed by a stringent regulatory authority, and as such, do not have sufficient evidence of their quality and safety. WHO is considering options to support these procurers in collaboration with its regional and country offices.

Watch list and active shortages

As mentioned above, the period of acute shortages has abated in most regions for the time being; however, given the potential for resurgences, WHO is still maintaining a watch list on the following products:

- 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

Substandard and falsified (SF) products

An update to previously issued Alert n5/2020 on falsified defibrotide is imminent. Defibrotide is used in clinical trials as a therapeutic of interest against covid19. Reports of SF remdesivir in the WHO regions of Europe (likely tampered) and South East Asia (likely falsified) have been received and reports of falsified azithromycin from PAHO.

Medical Devices

WHO Medical Devices Newsletter

The Newsletter provides updates and links to COVID-19 technical documents related to medical devices is available.

For those who are interested in receiving the newsletter, please email to LISTSERV@listserv.who.int with the words: SUBSCRIBE WHOMEDICALDEVICES in the body of the message.

June 2020 newsletter features:

1. Clinical Management of patients, *updated version*
2. The List of Priority Medical Devices for COVID, *describes the medical devices, the purpose and the settings where it can be used.*
3. The WHO technical specifications for Pressure Swing Adsorption Oxygen Plants
4. The role of imaging diagnostics

5. *Biomedical equipment Inventory tool for COVID*

   In the context of COVID-19, availability of essential equipment to provide oxygen and respiratory therapy to all countries, especially those that may have limitations in accessing global markets, is of utmost importance. WHO has developed a COVID-19 Biomedical Equipment Inventory Tool (survey) whose aim is to collect facility data on the availability of biomedical equipment (oxygen, accessories and consumables) and ventilators at the country level.

   The biomedical inventory survey for oxygen related devices:

   Username: biomedequipment, Password: facilityoxygen20

Please contact COVID-MED-DEVICES@who.int for support in implementing the survey, or any other information on medical devices for COVID.

Access to regulatory updates by WHO staff

All WHO staff have access to the Regulatory Updates at the following location:

P:\PubPersons\RPQ\COVID_Regulatory_Updates