Regulation of in vitro diagnostics, therapeutics, and vaccines
WHO Update – 10
Coronavirus disease 2019 (COVID-19)
22 May 2020

World Health Organization

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Key Messages

The World Health Assembly called upon International Organizations and other stakeholders to work collaboratively at all levels to develop, test, and scale-up production of safe, effective, quality, affordable diagnostics, therapeutics, medicines and vaccines for the COVID-19 response, including, existing mechanisms for voluntary pooling and licensing of patents to facilitate timely, equitable and affordable access to them.

Highlights and main issues

- WHO has developed a preliminary case definition and case report form for multisystem inflammatory disorder in children and adolescents temporally related to COVID-19
- Study of medicines utilization in COVID-19 affected pregnancy, and associations with pregnancy outcomes, was agreed by ICMRA as a priority to obtain real-world evidence to support regulatory decision making. Such studies should complement WHO studies on the natural history of COVID-19 infections in pregnancy
- Nine NAT assays are listed under the WHO EUL for IVDs
- The SOLIDARITY clinical trial is underway in 18 countries, representing over 245 hospitals with 885 clinicians involved and 3 000 patients enrolled
- WHO has published attributes and criteria that will be used to prioritize COVID-19 candidate vaccines to be considered for WHO's Phase IIb/III SOLIDARITY vaccine clinical trial
- Treatment of 5,000 patients with COVID-19 convalescent plasma was associated with a low rate of serious adverse reactions (allergic reactions, circulatory overload, acute lung injury) similar to those seen with non-immune plasma infusions, and enhancement of disease was not reported
- Please mark your diaries for 5th June! Moving to biweekly updates – new and improved version with hyperlinks to key information in previous versions

73rd World Health Assembly: Covid-19 Response

WHO convened ministers of health from almost every country in the world, the consistent message throughout the two-day meeting - including from the 14 heads of state participating in the opening and closing sessions - was that global unity is the most powerful tool to combat the outbreak.

A resolution, co-sponsored by more than 130 countries, was adopted by consensus. It calls for the intensification of efforts to control the pandemic, and for equitable access to and fair distribution of all essential health technologies and products to combat the virus. It also calls for an independent and comprehensive evaluation of the global response, including, but not limited to, WHO's performance.

The resolution is a concrete manifestation of the call for global unity, and a roadmap for controlling the outbreak.

The revised draft resolution (version 18 May 2020)

WHA Video recordings and relevant documents

Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19

Limited data describe clinical manifestations of COVID-19 that are generally milder in children compared with adults, but also show that some children do require hospitalization and intensive care. Recently, however, reports from Europe and North America have described clusters of children and adolescents requiring admission to intensive care units with a multisystem inflammatory condition with some features similar to those of Kawasaki disease and toxic shock syndrome.

Case reports and small series have described a presentation of acute illness accompanied by a hyperinflammatory syndrome, leading to multiorgan failure and shock. Initial hypotheses are that this syndrome may be related to COVID-19 based on initial laboratory testing showing positive serology in a majority of patients. Children have been treated with anti-inflammatory treatment, including parenteral immunoglobulin and steroids.

It is essential to characterize this syndrome and its risk factors, to understand causality, and describe treatment interventions. It is not yet clear the full spectrum of disease, and whether the geographical distribution in Europe and North America reflects a true pattern, or if the condition has simply not been recognized elsewhere.

There is therefore an urgent need for collection of standardized data describing clinical presentations, severity, outcomes, and epidemiology. WHO has developed a preliminary case definition and case report form for **multisystem inflammatory disorder in children and adolescents**. The preliminary case definition reflects the clinical and laboratory features observed in children reported to date and serves to identify suspected or confirmed cases both for the purpose of providing treatment and for provisional reporting and surveillance. The case definition will be revised as more data become available.

Scientific Brief: Multisystem inflammatory syndrome in children and adolescents

Alignment of approaches by regulatory groups

COVID-19 Real-World Evidence observational studies

The International Coalition of Medicines Regulatory Authorities (ICMRA) met on 19 May and discussed priorities for collaborative studies to obtain real-world evidence to support regulatory decision making.

Participants agreed that studies on COVID-19 affected pregnancies would be beneficial. Two proposed studies were presented: a WHO prospective longitudinal cohort study of health, pregnancy and birth outcomes of mother-infant pairs following maternal diagnosis of SARS-CoV-2 infection during pregnancy; and an European Medicines Agency (EMA) study of medicines utilisation in COVID-19 affected pregnancy,

and associations with pregnancy outcomes. Several regulators expressed interest in joining one or both studies. It was agreed the studies were complimentary and close cooperation between WHO and ICMRA would be important as the studies progressed.

The safety of medicines under evaluation, or authorized for use, for COVID-19 was agreed as a topic for collaborative observational study, as was preparedness for vaccine safety monitoring.

AVAREF

Building on to Ebola experiences, African Vaccine Regulatory Forum (AVAREF), together with National regulatory authorities and national ethics committees from across Africa, agreed to expedite clinical trial review and approvals for COVID-19 related products. This will be achieved through joint reviews, based on voluntary cooperation between the relevant national regulatory authorities and ethics committees.

Each country will remain solely responsible for granting regulatory approval.

How does it work?

- An online platform (SharePoint) to be used for joint reviews
- Participating countries post their queries online for real-time response from sponsors/applicants
- AVAREF to convene and coordinate virtual meetings for participating countries to conduct joint reviews of clinical trial applications on COVID-19
- Virtual meetings to be used to discuss pertinent issues on how regulators and ethics committees can better prepare and respond to the COVID-19 pandemic

AVAREF Tools for Processing clinical trial applications by Ethics Committees and National Regulatory Authorities in Africa

In vitro diagnostics

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. Applicants submit their applications for assessment based on WHO instructions for NAT and antibody detection rapid tests (RDTs) submissions.

38 submissions for NAT assays have been received so far.
The status of each application is presented here (19 May)

Nine 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
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.
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.

The new tests NAT assays WHO has listed under the emergency use listing procedure since the last update are:

- The **Novel Coronavirus (SARS-CoV-2) Real-Time Multiplex RT-PCR Kit manufactured by Shanghai ZJ Bio-Tech Co., Ltd.** is an in vitro diagnostic test for the qualitative detection of nucleic acid from the SARS-CoV-2 in upper and lower respiratory specimens (including nasopharyngeal or oropharyngeal swabs and sputum). The assay should be used in combination with the QIAamp Viral RNA Mini Kit manufactured by QIAGEN and the 7500 Real-time PCR Systems with SDS 2.3 software (Applied Biosystems; catalog #4351104 or #4351105) or 7500 Fast Real-time PCR Systems with SDS 2.3 software (Applied Biosystems; catalog #4351106 or #4351107).
- The **FTD SARS-CoV-2 manufactured by Fast Track Diagnostics Luxembourg S.à.r.l.** is a qualitative in vitro nucleic acid amplification test for the detection of severe respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acids in nasopharyngeal and oropharyngeal swabs of patients with signs and symptoms of SARS-CoV-2 infection in conjunction with clinical and epidemiological risk factors, who are suspected of Coronavirus Disease 2019 (COVID-19). The assay was validated for use with the NucliSENS® easyMAG® (bioMérieux) and the Thermo Fisher Scientific Applied Biosystems® 7500 Real-Time PCR System.
- The **Multiple Real-Time PCR Kit for Detection of 2019-CoV manufactured by Beijing Applied Biological Technologies Co., Ltd.** is an in vitro diagnostic medical device, based on real time RT-PCR technology utilizing reverse-transcriptase (RT) reaction to convert RNA into complementary DNA (cDNA). It is intended for the qualitative detection of 2019-nCoV RNA. Oropharyngeal swab and sputum specimens are validated for use. The assay is manually operated.

Antibody detection rapid tests have been eligible for WHO emergency use assessment since 17 April. WHO recently received the second expression of interest for an antibody detection RDT and several pre-submission calls have been held with manufacturers interested in submitting for EUL assessment. WHO is currently working on the development of instructions for submission of antibody detection enzyme immunoassays (EIAs) and antigen detection RDTs. These will be published soon on the WHO website and the EUL eligibility expanded to such products.

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 (18 May)

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

WHO Solidarity Clinical Trial

The Solidarity trial is an international clinical trial to help find an effective treatment for COVID-19, launched by the WHO and partners.

Over 100 countries have expressed an interest in participating in the trial and WHO is actively supporting more than 60 of them, including with the following:

- ethical and regulatory approvals of the WHO core protocol;
- identification of hospitals participating in the trial;
- training of hospital clinicians on the web-based randomization and data system;
- shipping the trial drugs as requested by each participating country.

To date, 18 countries, from five out of the six WHO regions and representing three out of the four World Bank income groups, have started the Solidarity Trial. These 18 countries represent over 245 hospitals with 885 clinicians involved and 3 000 patients enrolled. Another 10-12 countries are expected to start the trial in the coming weeks.

An interim trial analysis will be produced and will be monitored by an independent group of experts as the global Data and Safety Monitoring Committee (DSMC).

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

Since the last analysis (summarised in WHO Regulatory Update No. 9), 353 new case reports were submitted to VigiBase, the WHO Global database of Individual Case Safety Reports. Most of the reports describe at least one drug or substance in the WHO Solidarity trial as either suspected or interacting.

The reported ADRs largely continue to be those included in available product labelling or information; QT prolongation and hepatic events are the most commonly reported events. Of note are the concomitant use of multiple interacting medications and the occurrence of individual cases of serious events such as drug rash with eosinophilia and systemic symptoms (DRESS), completed suicide and sudden death which will remain under surveillance in future reviews.

Cumulatively, there are now a total of 1 491 reports on the Solidarity Trial Drugs, from five WHO regions, with most of the reports coming from the European region. Of interest, there are a total of 67 reports of remdesivir in VigiBase of which 10 were reported in the current review period.

A short summary of every one of the 10 new case reports with remdesivir, together with a descriptive analysis of the other new reports is available: Descriptive analysis (19 May)

Vaccines

Criteria for COVID-19 vaccine prioritization

WHO has published attributes and criteria that will be used to prioritize COVID-19 candidate vaccines to be considered for WHO's Phase IIb/III clinical trial. The attributes that will be used are the safety profile of the candidate; its potential for efficacy; the candidate vaccines stability; vaccine implementation considerations; and availability of a successful candidate. Criteria that are considered of major importance in ranking the vaccines are identified in the document.

WHO will also provide a scoring guide to promote consistency and predictability of evaluation. The target audience includes vaccine scientists, product developers, manufacturers, regulators and funding agencies.

Criteria for COVID-19 vaccine prioritization (17 May)

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 (22 May)

Convalescent plasma

Limited early reports of uncontrolled empirical use of COVID-19 convalescent plasma in settings of severe and life-threatening COVID-19 so far have documented favourable outcomes in patients. In particular, treatment of 5,000 patients with COVID-19 convalescent plasma was associated with a low rate of serious adverse reactions (allergic reactions, circulatory overload, acute lung injury) similar to those seen with non-immune plasma infusions, and enhancement of disease was not reported.

Positive historic experience with use of convalescent plasma to treat SARS and pandemic influenza further supports the plausibility of a clinical benefit in COVID-19. Moreover, a Cochrane rapid systematic review on the use of COVID-19 convalescent plasma and hyperimmune immunoglobulin provides information on case series and on studies that have been registered in clinical trial websites. The outcomes of the rapid review reinforce that COVID-19 convalescent plasma should be used in randomized controlled trials (RCTs) as the most effective and efficient strategy to determine the efficacy and safety of this experimental therapy.

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

WHO Working Group on Assays and Reference Preparations

The 20 May meeting discussed whether passage of SARS-CoV-2 virus isolates in cell culture selected for viruses that were significantly different from viruses circulating in the community. One laboratory discovered that a single cell-culture passage in the laboratory had resulted in a 26 base-pair deletion in the spike protein. The group discussed whether use of this virus in neutralization tests to evaluate vaccine clinical trials might give misleading results. It was concluded that more data are required to address this issue, preferably collected through the upcoming WHO international collaborative study of candidate serological reagents being organized by NIBSC, UK.

The development of SARS-CoV-2 reporter viruses was also reported. These are wild-type viruses that have been genetically engineered to express either luciferase activity or to fluoresce. Data were presented to show the reporter viruses gave comparable results to the parental wild-type virus in functional serological assays, such as neutralizing antibody tests. The advantage of using a reporter virus is that the neutralization test could be automated, and thus achieve a greater through-put of samples. A theoretical advantage of a reporter virus is that because it retains all SARS-CoV-2 proteins it would give a more comprehensive read-out of the antibody repertoire generated by candidate vaccines compared to assays that use pseudotype viruses, which would assay the S-protein response only.

WHO Working Group on Animal Models

The 21 May meeting discussed availability of the hACE2 transgenic mouse model. The US Jackson Laboratory has built a colony of hemizygous hACE2 tg mice which will be available for widespread distribution from mid-June. Some distribution has already occurred to laboratories in the US and in China. The mice are available at cost, and with a simplified ordering process. The Jackson Laboratory is also building a homozygous hACE2 transgenic colony. Initial results suggest that the hemizygous mouse phenotype is sufficient for experiments with SARS-CoV-2 virus.

Results of an immunization/challenge experiment in rhesus macaques was also reported. Six spike-protein variant DNA constructs were used to immunize animals. The constructs were built for scientific investigation, not for clinical development. All constructs stimulated neutralizing antibody and T-cell responses, but some constructs gave stronger responses than others. A spectrum of protection was seen after challenge. Membrane-anchored trimeric spike constructs gave the best protection, consistent with other findings. Protection against virus replication in lungs was observed, and there was a statistically significant correlation between serum neutralizing antibody titre and protection as assessed by sub-genomic virus RNA titre in bronchiolar lavage samples. However, virus replication occurred in the upper respiratory tract of immunized animals. The reason for the lack of protection in the nasal cavity is not yet elucidated.

Substandard and Falsified products

WHO continues to receive reports of substandard and falsified (SF) products in relation to the Covid19 outbreak, either because demand has increased or because supply has been constrained. Vigilance is requested from all regulators.

Supply chain updates from WHO HQ and Reginal Offices

Customs and trade

A list of priority items has been developed and transmitted to customs authorities *and is available on the following link:*

http://www.wcoomd.org/en/media/newsroom/2020/april/who-wco-list-of-priority-medicines-and-an-updated-joint-wco-who-hs-classification-list.aspx

Shipments from UN partners:

Challenges with transportation continue to affect shipments in many regions. Reports are the availability of flights for transporting goods has improved in North America, Europe, and to some extent into and out of India. Other regions continue to experience problems with transportation. Shipments to countries continue

from the UN supply chain consortium; however, the availability of some products remains limited. Items procured include PPE and oxygen concentrators and diagnostics supplies. Note that medicines for use in eligible clinical trials are not included and should be referred to teams managing the Solidarity Trials.

Shortages:

WHO continues to monitor shortages across regional networks, industry associations and regulatory networks. Supplies levels have continued to improve with certain supplies remaining constrained but not in shortages. The information is from North America, Western Europe, and limited countries in the Eastern Mediterranean Region.

Production capacity in India remains at 70% of normal, with no backlogs in domestic or export orders. Domestic transportation has been improved for intra-country movement in India and flights for export are improving as well. Most countries are considering reserve stock as a preventative measure, either for a second wave or to increase current treatment capacity. Global and national allocation approaches are under development.

The following medicines remain in constrained supply:

- Antibiotics: azithromycin, levofloxacin, metronidazole, amoxiclav, piperacillin, tazobactam
- Renal replacement fluids
- 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) note: problems with API are the cause of the constraints with the latter two products.
- HIV: Lopinavir/ritonavir
- NCD: Metformin

Other products remaining constrained:

- *Blood and plasma:* In some countries, particularly in areas where clinical trials of convalescent plasma are underway, there are reports of shortages in blood and plasma supply. The shortage is in part due to the unavailability of donors in lockdown measures and also an increase in use.
- *PPE:* supplies remain strained
- *Oxygen and ventilators:* remain in shortage for a number of countries.

Export restrictions

Export restrictions have been reduced, including restrictions from European countries.

Medical Devices

African Medical Devices Forum (AMDF)

AMDF, Technical Committee under the African Medicines Regulatory Harmonization (AMRH) Initiative, is responding to COVID by establishing a COVID-19 Task Force with 4 working sub-groups:

1. Prepare list of commercial COVID-19 in vitro diagnostics tests which have been assessed using various regulatory approaches to confirm acceptable quality, safety and performance.
2. Prepare list of selected medical devices and protective, preventive equipment used in COVID-19 management.
3. Propose mechanism(s) to receive information on substandard and falsified diagnostic tests and other medical devices and dissemination of such information to regulators on the continent.
4. Prepare a guidance document on management of IVDs and medical devices donations for COVID-19.

AMDF – Report (April)

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