Regulation of *in vitro* diagnostics, therapeutics, and vaccines
WHO Update – 4
Coronavirus disease 2019 (COVID-19)
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World Health Organization

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Key Messages

WHO is committed to ensuring that as medicines, vaccines and other health products are developed, they are shared equitably with all countries and people. The Director-General indicated WHO's support for a Costa Rican proposal to create a global pool for rights in COVID-19 related technologies.

WHO is calling on regulators to take a unified approach to regulatory flexibilities to facilitate access to diagnostics, medicines and vaccines.

Highlights and main issues

- So far, more than 90 countries are engaging, or have expressed an interest, in the Solidarity Trials announced by the WHO DG on the 18th of March.
- If outcomes from the SOLIDARITY trials provide new scientific evidence on effectiveness of candidate therapeutics against SARS-CoV-2, an emergency meeting of the Expert Committee on Essential medicines will be convened as quickly as possible.
- The third clinical trial of a candidate SARS-CoV-2 vaccine has been initiated. The new candidate, a DNA vaccine, is being tested in the USA.
- Three IVDs, the *genesig Real-Time PCR Coronavirus (COVID-19*) and *cobas SARS-CoV-2 Qualitative assay for use on the cobas® 6800/8800 Systems,* and *RealTime SARS-CoV-2 assay m2000 System (rRT-PCR test)* have been listed by WHO PQ for emergency use.
- Falsified chloroquine products have been identified in multiple African countries and a global alert was issued on 9 April.
- Lists of the most relevant existing WHO guidance documents in the area of quality assurance and regulatory guidelines to support the development, production and evaluation of candidate SARS-CoV-2 vaccines and candidate medicines have been published.
- A new expanded section on medical devices will be included in future updates.

Enabling equitable access of medicines, diagnostics and vaccines

The Medicines Patent Pool and UNITAID announced an initiative on 3rd April to include medicines and diagnostics for COVID-19 in their licensing pool[1].

Costa Rica developed a proposal to create a pool of rights to tests, medicines and vaccines, with free access or licensing on reasonable and affordable terms for all countries. WHO supports this proposal, and is working with Costa Rica to finalize the details.

WHO is committed to ensuring that as medicines and vaccines are developed, they are shared equitably with all countries and people. Poorer countries and fragile economies stand to face the biggest shock from this pandemic and leaving anyone unprotected will only prolong the health crisis and harm economies more. At the opening of the G-20 virtual world summit on 26 March, the DG called[2] on all countries, companies and research institutions to support open data, open science and open collaboration so that all people can enjoy the benefits of science and research.

Sharing information with regional regulatory groups

On 09 April 2020, WHO HQ and PAHO jointly held a meeting with the NRAs of the Americas. The objectives of the meeting were:

- Sharing WHO regulatory updates, clarify any regulatory questions around vaccines, therapeutics and diagnostics.
- Identify the regulatory challenges around COVID-19 and provide guidance to the National Regulatory Authorities on regular basis through focal points to address those regulatory challenges.

The meeting was attended by 98 participants, representing countries from Canada to Argentina. A presentation giving a global regulatory update from WHO was followed by a Q&A session. Topics raised in the Q&A included specifications for devices especially ventilators and face masks; rapid detection tests for SARS-CoV-2; specifications for convalescent plasma; the type of interferon being recommended in the SOLIDARITY trail; and mechanisms to share the WHO regulatory update with NRAs. Some questions were answered in the meeting, others will be followed-up by PAHO and WHO.

PAHO will organise future meetings of the regional regulatory group every two weeks, with a focus on a specific regulatory topic in each meeting. WHO HQ will also join when requested.

In vitro diagnostics

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

[1] medicinespatentpool.org/mpp-media-post/the-medicines-patent-pool-and-unitaid-respond-to-access-efforts-for-covid-19-treatments-and-technologies/

[2] www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-g20-extraordinary-leaders-summit-on-covid-19---26-march-2020

other useful information on policies and guidance. 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.

The most recent update was published on 6 April. New information from China was added. The links can be found at:
www.who.int/diagnostics_laboratory/200406_imdrf_covid19_listing_update_6_april_2020.pdf?ua=1

WHO EUL for SARS-CoV-2 virus IVDs

The WHO Prequalification Team is assessing products for Emergency Use Listing (EUL) for candidate in vitro diagnostics (IVDs) to detect SARS-CoV-2. Currently, assays for the detection of SARS-CoV-2 nucleic acid are eligible for EUL assessment.

On 9 April 2020 WHO listed a third product under the Emergency Use Listing procedure for in vitro diagnostics. The **Abbott RealTime SARS-CoV-2 assay** is a real-time reverse transcription polymerase chain reaction (rRT-PCR) test **on the Abbott m2000 System**. The SARS-CoV-2 primer and probe sets are designed to detect RNA from SARS-CoV-2 in nasopharyngeal and oropharyngeal swabs from patients with signs and symptoms of infection who are suspected of COVID-19.

More information on the product will be published on the WHO website in the coming days.

An additional 31 submissions have been received by WHO and are being assessed. At least another 9 submissions are expected.

Information on applications received, which is updated weekly, can be found at:
www.who.int/diagnostics_laboratory/200407_eul_covid19_ivd_update.pdf?ua=1

Advice on the use of point-of-care immunodiagnostic tests for COVID-19

A new Scientific Brief[3] was published on 08 April 2020 in response to the growing COVID-19 pandemic and shortages of laboratory-based molecular testing capacity and reagents, multiple diagnostic test manufacturers have developed and begun selling rapid and easy-to-use devices to facilitate testing outside of laboratory settings. These simple test kits are based either on detection of proteins from the COVID-19 virus in respiratory samples (e.g. sputum, throat swab) or detection, in blood or serum, of human antibodies generated in response to infection.
At present, based on current evidence, WHO recommends the use of these new point-of-care immunodiagnostic tests only in research settings. They should not be used in any other setting, including for clinical decision-making, until evidence supporting use for specific indications is available
WHO applauds the efforts of test developers to innovate and respond to the needs of the population. However, before these tests can be recommended, they must be validated in the appropriate populations and settings. Inadequate tests may miss patients with active infection or falsely categorize patients as having the disease when they do not, further hampering disease control efforts.

WHO continues to evaluate available immunodiagnostics tests for COVID-19 and will update this scientific brief when necessary.

3 www.who.int/news-room/commentaries/detail/advice-on-the-use-of-point-of-care-immunodiagnostic-tests-for-covid-19

Therapeutics

SOLIDARITY clinical trials for COVID-19 treatments and new developments

So far, more than 90 countries are engaging, or have expressed an interest, in the Solidarity Trials announced by the WHO DG on the 18th of March. The aims of the solidarity trial are to:

- use the same or similar protocols across different countries,
- allow data to be reviewed / compared from the same viewpoint and rapidly discover whether any of the drugs slow disease progression or improve survival,
- provide simplified procedures to enable overloaded hospitals to participate without additional required paperwork

Treatment options currently under study are:

Remdesivir was previously tested as an Ebola treatment. It has generated promising results in animal studies for Middle East Respiratory Syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS), which are also caused by coronaviruses, suggesting it may have some effect in patients with COVID-19.

Lopinavir/Ritonavir is a licensed treatment for HIV. Evidence for COVID-19, MERS and SARS is yet to show it can improve clinical outcomes or prevent infection. This trial aims to identify and confirm any benefit for COVID-19 patients. While there are indications from laboratory experiments that this combination may be effective against COVID-19, studies done so far in COVID-19 patients have been inconclusive.

Interferon beta-1a is used to treat multiple sclerosis.

Chloroquine and **hydroxychloroquine** are very closely related and used to treat malaria and rheumatology conditions respectively. In China and France, small studies provided some indications of possible benefit of chloroquine phosphate against pneumonia caused by COVID-19 but need confirmation through randomized trials.

Further information is available at:
www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments

WHO will soon launch a COVID-19 seroepidemiology study, as part of the Solidarity Trial efforts, named Solidarity II. The Solidarity II study goes hand-in-hand with WHO Unity Studies, as it aims at designing a master protocol for these Early Investigation Protocols. WHO has made core protocols available to all countries to rapidly and systematically collect and share data on transmission patterns, severity, clinical features and risk factors for infection and other virus characteristics, in a format that facilitates aggregation, tabulation and analysis across different settings globally. More than 40 countries are already using the Unity Studies.

Solidarity III will be another study which will look specifically at the role of therapeutics in COVID 19 prophylaxis and post-exposure prophylaxis in health care workers.

WHO Working Group on therapeutics

The Working Group meets regularly to review emerging evidence on potential treatment options. The most recent published meeting report is summarized here.

Informal consultation on the role of therapeutics in COVID-19 prophylaxis (PrEP) and post-exposure prophylaxis (PEP)

An expert consultation on 31 March 2020 convened clinical care partners and experts in the field of randomized controlled trials (RCTs), biostatistics, regulatory affairs, preclinical studies, and pharmacology to evaluate current progress in the area of COVID-19 chemoprophylaxis.

A Mahidol University, Thailand, study is a randomized placebo-controlled trial of 40,000 healthcare workers (HCW) in Southeast Asia, also being extended to South Africa, Malawi, Uganda, Kenya, Niger, Cameroon and DR Congo. The study is scheduled to start recruiting participants in two weeks. This protocol is robust and could be considered as the basis for a core healthcare worker protocol. However, the dose of hydroxychloroquine proposed in the Mahidol study needs further discussion. Modelling analysis done by the Gates foundation predicts that there would be a major challenge ensuring the global supply of hydroxychloroquine for use in healthcare workers at the dose currently proposed in the Mahidol study (daily dosing).

The CROWN CORONATION (Chloroquine Repurposing for Healthcare Workers for Novel Coronavirus Mitigation) Trial is an international multicentre trial with a primary focus on Africa, but also New Zealand and the United Kingdom. The study is based on pre-exposure prophylaxis. There are > 200 African sites represented in the study. The study also aims to determine the optimal dose of chloroquine; hence, three different doses (high, medium, and low) would be tested compared to placebo. Overall, 55,000 healthcare workers are expected to be randomized.

The Consultation noted that there is currently variation in the endpoints of planned prophylactic clinical trials. Having a harmonized endpoint and a common DSMB is critical. The studies assessing prophylaxis are looking at both the prevention and mitigation of disease as main objectives. Both are relevant and important factors to be captured.

Concerning PEP, several studies have already started and might deliver results rapidly, therefore informing further follow-on studies. Careful planning for next steps should be paramount to make sure there is a shared common approach for follow-on studies.

The Consultation concluded that for the development of core protocols for chemoprophylaxis, further work is needed and subgroups were established on PrEP in HCW; PEP in household and ring approach settings; and chloroquine dosing. The Working Group will meet again within two weeks.

A report of the meeting is at:
www.who.int/blueprint/priority-diseases/key-action/informal-consultation-therapeutics-covid19-prophylaxis.pdf?ua=1

Model List of Essential Medicines

The WHO Expert Committee on the Selection and Use of Essential Medicines is responsible for updates the Model List of Essential Medicines. An emergency session of the Expert Committee was convened in 2010 during the H1N1 pandemic dedicated to the assessment of antivirals (oseltamivir, zanamivir, amantadine and rimantadine).

The EML Secretariat is monitoring RCTs and R&D for medicines against COVID-19 disease or COVID-19 symptoms to identify potential candidates for inclusion on the Model List. Some candidate therapeutics,

such as chloroquine and hydroxy chloroquine, are included on the Model List, but for indications other than COVID-19.

If outcomes from the SOLIDARITY trials provide new scientific evidence on effectiveness against SARS-CoV-2 an emergency meeting of the Expert Committee will be convened as quickly as possible. This will particularly important if highly-priced medicines being trialled for COVID-19 (eg, tocilizumab and IL-6 or IL-1 inhibitors) demonstrate benefit.

ICMRA virtual meeting on therapeutics and ongoing/planned trials

ICMRA have published a report of their 2 April 2020 meeting highlighting regulatory considerations on the development of potential COVID-19 therapeutics, clinical trials and compassionate use programmes.

At this point in time, no medicine has yet clearly demonstrated efficacy in treating COVID-19. Workshop participants stressed that the fastest way to serve patients was to collect robust evidence to determine which investigational agents or repurposed medicines would be safe and effective for the treatment of COVID-19.

Regulators agreed that multi-centre randomised controlled studies are the best way to generate the data required to enable rapid development and approval of potential treatments for COVID-19. They also agreed on a harmonised approach to make best use of the available supply.

Participants committed to exchange information about the ongoing studies and results to support the global approach. ICMRA will convene another regulatory workshop to discuss the progress on COVID-19 medicine development in the coming months.

The report of the meeting is available at: http://www.icmra.info/drupal/en/news/9April2020

ICMRA virtual meeting on real world evidence observational studies

On 6 April 2020, 93 participants from more than 25 NRAs joined a virtual meeting organized by ICMRA to share information on planned, initiated and completed observational studies to characterize Covid-19 disease and any link between clinical outcome and concomitant medication use.

The meeting heard that several studies were completed already, and others are close to completion. This shows that observational studies can be done, and answers obtained, quickly. Observational studies to help evaluate the safety and effectiveness of SARS-CoV-2 vaccines and treatments, when these become available, were also discussed. A report of the meeting will be available as soon as possible and more details will be shared in the next update.

WHO support to accelerate access to candidate medicines for COVID-19

Relevant WHO guidance for SARS-CoV-2 COVID-19 Treatment - medicines

The secretariat has reviewed and published a list of existing WHO guidance documents adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) and published in the Technical Report Series. The listing collects in one place the most relevant WHO guidance in the area of pharmaceutical quality assurance and regulatory guidelines for medicines. It is intended to support the

development, production, evaluation, and distribution of medicines for COVID-19 treatment. This list is organized following the different product-lifecycle phases and tools provided by WHO.

Further information can be requested from the secretary of the ECSPP, Dr Sabine Kopp (kopps@who.int)

link to the list is at: https://www.who.int/medicines/areas/quality_safety/quality_assurance/en/

Vaccines

Third clinical trial of a candidate SARS-CoV-2 vaccine.

A new SARS-CoV-2 vaccine candidate has entered Phase 1 clinical human testing in the USA. The INO-4800 DNA vaccine candidate produced promising results in preclinical animal immunogenicity studies. The DNA vaccine candidate will initially be tested in 40 healthy volunteers. DNA vaccines, while available and approved for a variety of animal infections in veterinary medicine, have not yet been approved for human use.

Landscape of candidate vaccines for SARS-CoV-2

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

The 4 April 2020 version is available at:
www.who.int/blueprint/priority-diseases/key-action/Novel-Coronavirus_Landscape_nCoV-4april2020.pdf?ua=1

WHO support to accelerate access to candidate SARS-CoV-2 vaccines

WHO documents that are relevant to development, production and evaluation of SARS-CoV-2 vaccines and potential biological therapeutics

The secretariat has reviewed and published a list of existing WHO guidance documents adopted by the WHO Expert Committee on Biological Standardization (ECBS) and published in the Technical Report Series. The listing collects in one place WHO written standards that may provide useful guidance and information for the development, production and evaluation of candidate SARS-CoV-2 vaccines. The list is not exhaustive but focused on evaluation of the quality, safety and efficacy of vaccines. Some WHO guidelines may also be applicable for other COVID-19 interventions such as candidate biological therapeutic products (e.g. antibodies). WHO will continue to update this list.

Further information can be requested from the secretary of the ECBS, Dr Ivana Knezevic (knezevici@who.int).

The list is available at: https://www.who.int/biologicals/en/

Blood supply and use of blood components in the response to COVID-19

Convalescent plasma trials

WHO continues monitoring the increasing interest of several countries in using convalescent plasma as a therapeutic for COVID19, in liaison with the WHO Blood Regulator Network, the WHO R&D Blueprint Working Group on Therapeutics and WHO partners (EU, ECDC, CoE/EDQM, ISBT)
Countries conducting clinical trials for convalescent plasma (CP) include Canada, China, Germany and USA, WHO has been informed that protocols have been developed by Argentina, Saudi Arabia and Philippines. In USA and Canada both CTs and compassionate use are occurring, but in different parts of the country.

A dedicated website of ISBT provides information on convalescent plasma and can be found at:
http://isbtweb.org/index.php?id=1493

Enabling research; animal models, clinical trial protocols, assay development, standards

WHO Working Group on Assays and Reference Preparations

The UK's NIBSC, a WHO CC, is preparing reference reagents for COVID-19. One set of reagents are for SARS-CoV-2 RNA. A research reagent, catalogue number 19/304, which is full length SARS-CoV-2 genome RNA packaged into HIV-like particles is now available. Candidate WHO International Standards are also in preparation. NIBSC are recruiting participants for an international collaborative study to characterize the candidate materials.

A second set of reagents are for SARS-CoV-2 antibodies. Donations of convalescent plasma from 11 UK patients have been received and are being processed to prepare a reference reagent, which is expected to be available at the end of April. Candidate WHO International Standards for SARS-CoV-2 antibodies are also in preparation. NIBSC are recruiting participants for an international collaborative study to characterize the candidate materials.

WHO Working Group on Animal Models

The Group has been requested to assist in the screening of candidate therapeutics to be included in the second round of the WHO SOLIDARITY trial. Literature reviews and analysis of *in vitro* data of existing drugs that could be repurposed for use against SARS-CoV-2 has resulted in a long list of a hundred or more potential candidates. Testing in animals of the potential candidates could help reduce the long list to a short list. However, in order for this to happen, it will be necessary to agree on a testing strategy including, but not limited to, factors such as choice of animal model, common protocols, and a coordination strategy to efficiently work through the list. The Group agreed to work on this.

A study in mice was reported that showed excess mortality for animals treated with a combination of metformin and hydroxychloroquine. The relevance of this study to humans is not yet clear.

A study of SARS-CoV-2 infected hACE transgenic mice treated with Pudilan Xiaoyan oral liquid (PDL), a traditional Chinese medicine consisting of four herbs, showed a significant benefit for animals treated

with PDL. PDL is used for the treatment of influenza-like symptoms and is being studied in China in COVID-19 patients, but no data are yet available.

Supply chain

Travel impact on shortages:
The impact of the combine transportation restrictions with the confinement approach to curbing transmission is having a compounding effect on deliveries in and out of India. Informal estimates indicate that some factories are still working, but at reduced capacity. In addition to limited air transport capacity, there are concerns about the impact of limited ground transport to move products to ports of export. Letters issued by WHO and ICAO are having some positive impact, but concerns remain.

Speculative procurement:
Export restrictions remain an issue, increasing competition for supply of products. UN procurement will be streamlined to avoid any fragmentation in the humanitarian sector; however, fragmentation and speculative procurement of products currently in clinical trials continue through private and bi-lateral procurement channels. For manufacturers who need to scale up, the false demand signals will create difficulties in estimating production needs.

Transportation cost increases:
Transportation costs continue to increase. Medical supplies are often smaller shipments and are deprioritized over other larger cargo, exacerbating the problem.

Supply chain networks:
There are an increasing number of supply chain networks developing to support countries, quantification activities and gather market knowledge. These groups are useful and a mapping was recently conducted. The mapping will be used in the future as tool to share key deliverables and contacts for these groups.

Specific products:
WHO meets on a weekly basis with regulators, industry associations and UN partners on the status of a key list of medicines. Medicines for ICU care, including anesthetics and antibiotics are showing signs of shortages in certain markets. Experimental medicines, including chloroquine, hydroxychloroquine, and lopinavir/ritonavir remain subject to speculative buying as well as falsified and substandard products. In cases where alternative therapies are clinically appropriate and available, they may provide a mitigation strategy subject to national guidelines.

Local production:
There is significant interest in converting existing local manufacturing capacity to produce personal protective equipment (PPEs) and other supplies. Technical specifications for some products are available and quality standards should be a priority.

Donation programs:
There are increasing numbers of donations offers, including bi-lateral and corporate donations. The WHO guideline on donations provides practical considerations for making donations. Of note, it is critical to avoid donations that will not be of immediate help or that will burden the health system.

Falsified and substandard products

On 31 March, WHO issued a warning against an increased number of falsified medical products in relation to the management of Covid19. On 08 April WHO issued a medical product alert regarding falsified chloroquine products that have been identified in multiple African countries. The recent media attention on the use of (hydroxy)chloroquine to treat Covid19 has led to a strong increase in the demand for this product. We have also received multiple reports regarding a steep increase in the prices of API or finished products of (hydroxy)chloroquine.

The link to the medical product alert is at: WHO Global Medical Product Alert.

On 9th April, WHO issued an alert relating to incidences of Falsified Chloroquine.
www.who.int/news-room/detail/09-04-2020-medical-product-alert-n4-2020
We continue to request exertion of due diligence and vigilance throughout the supply chains and encourage reporting any suspected or confirmed substandard or falsified medical products to rapidalert@who.int

In addition, WHO has issued an information that provides guidance on how to assess the authenticity of nucleic acid testing assays and serology assays for SARS-CoV-2. This document targets end-users of IVDs, procurement entities and customs officials, national programme managers and their implementing partners, national regulatory authorities for IVDs.

Medical Devices (to be expanded in future updates)

Africa Medical Devices Forum (AMDF) COVID-19 Task Force

WHO has been supporting the African Medicines Regulatory Harmonization (AMRH) initiative through the Africa Medical Devices Forum (AMDF) Technical Committee to address regulatory challenges facing regulators in Africa in responding to the COVID-19 pandemic. On 2nd April 2020, AMDF established a COVID-19 Task Force to provide technical advice and provide recommendations to the AMDF Technical Committee and subsequently to the AMRH Steering Committee (SC) including National Regulatory Authorities (NRAs).

The work of the AMDF Task Force is undertaken by selected experts from NRAs, National Public Health Laboratories and Research Institutes in Africa. The Taskforce is supported by WHO experts and it works in four priority areas: In vitro diagnostics tests for COVID-19; medical devices and personal protective equipment (PPEs); substandard and falsified IVDs, medical devices and PPEs; and donations.
Activities being undertaken by the Task Force include developing:

1. List of tests including names and sources (manufacturer`s contact details) including WHO Emergency Use Listing Procedure (EUL).
2. List of medical devices and other products for prevention, control and case management (names and sources (manufacturer's contact details).
3. 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. Guidance document on management of IVDs and medical devices donations for COVID-19.

The Task Force has been working from 6th to 9th April 2020 and is expected to provide feedback to the AMRH SC and other AMRH partners on 14th April 2020. The AMRH SC will provide feedback to Member States through the Joint Secretariat (WHO & AUDA-NEPAD).