Regulation of *in vitro* diagnostics, therapeutics, and vaccines
WHO Update – 3
Coronavirus disease 2019 (COVID-19)
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World Health Organization

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Key Messages

First WHO EUL listing

On 3 April WHO listed the first in vitro diagnostic for COVID-19. The cobas SARS-CoV-2 Qualitative assay for use on the cobas® 6800/8800 Systems is manufactured by Roche Molecular Systems, Inc. The test can be used in nasopharyngeal and oropharyngeal swab samples from patients who meet the SARS-CoV-2 clinical criteria, to aid in the diagnosis of SARS-CoV-2 infection. It utilizes the cobas® 6800/8800 Systems, which are fully automated systems for sample preparation (nucleic acid extraction and purification) followed by PCR amplification and detection. WHO listed the product based on the submitted evidence including documentary evidence from the technical file and quality management system.

RDTs

Based on the currently available information WHO does not recommend the use of antibody and antigen detection assays in clinical diagnosis. However, several member states have expressed interest in serological rapid diagnostic tests. A number of national regulatory authorities members of the International Medical Device Regulators Forum (IMDRF) have assessed and listed serological tests. WHO is giving due consideration to newly available evidence.

Therapeutics

The public demand for identifying effective COVID-19 therapies to treat critically ill patients is leading many countries to initiate multiple small studies and compassionate use of candidate therapeutics of unknown or partially known effectiveness for treatment. It is important that large randomized controlled trials of high quality be initiated to generate the most robust data for timely regulatory decisions. Nonetheless it is important that regulators are aware and informed of data on candidate therapies from compassionate use programmes. Some countries are investigating the role of patient registries to capture data from outside trial settings. The important role of vigilance and adverse event reporting systems should also be stressed.

Highlights and main issues

- Platforms for sharing information with regional regulatory groups
- More than 80 countries have expressed interest in taking part in the Solidarity trial of therapeutics
- Regulators in many countries report being swamped with applications for COVID-19 interventions

- Due to supply chain issues LMICs in particular are having difficulties finding sources for core lists of medicines.
- Experimental medicines, including chloroquine and hydroxychloroquine remain subject to speculative buying and there are also reports of misuse as well as falsified and substandard products.

Platforms for sharing information with regional regulatory groups

African regional regulatory groups

In the context of its technical support to AMRH Continental Technical Working Groups (Expert Working Groups) WHO is establishing electronic platforms based on MedNet for exchange of regulatory information and support of joint activities related with COVID-19. The African Vaccines Regulatory Forum (AVAREF) and African Medical Devices Forum (AMDF) will be the first two regulatory networks in Africa to use this instrument, with the expectation to enrol it to other AMRH EWGs.

In vitro diagnostics

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

9 countries (Australia, Brazil, Canada, China, Japan, Russia, Singapore, South Korea, USA) have listed IVDs for diagnosis of COVID-19 on the basis of expedited regulatory assessments. To help other countries, WHO published links to these emergency lists, together with contact details. The links provided present information on IVDs authorized for use in the International Medical Device Regulators Forum (IMDRF) jurisdictions along with 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.** WHO will provide updated versions as new information becomes available.

The links can be found at:
https://www.who.int/diagnostics_laboratory/200402_imdrf_covid19_listing_update_2_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. WHO has received 30 expressions of interest under the EUL assessment for IVDs. For 20 products manufacturers have submitted applications; all 20 submissions are undergoing screening and review.

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Information on applications received, which is updated weekly, is summarized below and can be found at:
www.who.int/diagnostics_laboratory/EUL/en/

Summary table: 03 April 2020

Product type: NAT		
Stage of process	QMS review	Documentary evidence review
Total EOI	30	30
Awaiting submission	10	11
In process = i.e. Total EUL applications in screening phase and in the review phase/total applications received	20/20	18/19
In process and additional information requested from manufacturer (as part of QMS or dossier review i.e. after PEC assessor review)	4	3
Stage complete	1	1
Number of products with EUL listing	1	

Serology and RDTs

Based on the currently available information WHO does not recommend the use of antibody and antigen detection assays in clinical diagnosis. The WHO Laboratory testing strategy recommendations for COVID-19 provide the following advice:

Serological assays will play an important role in research and surveillance but are not currently recommended for case detection and are not included in this document. The role of rapid disposable tests for antigen detection for COVID-19 needs to be evaluated and is not currently recommended for clinical diagnosis pending more evidence on test performance and operational utility. WHO will update this guidance as more information laboratory tests for COVID-19 becomes available.

However, several member states have expressed interest in serological rapid diagnostic tests. A number of national regulatory authorities members of the International Medical Device Regulators Forum (IMDRF) have assessed and listed serological tests. WHO is giving due consideration to newly available evidence.

WHO Collaboration with FIND

FIND are collating the pipeline of diagnostic tests for SARS-CoV-2, and also in the process of conducting an independent evaluation of both molecular tests and immunoassays, in collaboration with WHO. Products are being selected for evaluation through expressions of interest (EOI). The first EOI for developers of *in vitro* diagnostics (IVDs) that detect SARS-CoV-2 nucleic acid (molecular assays) resulted in over 200 submissions and the evaluations are now underway. A second call for test developers interested in having their immunoassays (manual ELISA, machine-based or lateral flow, rapid tests specific for SARS-CoV-2 antigen or antibodies) closed on 20 March 2020 with nearly 100 submissions. Data from these standardized evaluations will be made publicly available to assist in-country decision making. For further information see:

https://www.finddx.org/covid-19/

Therapeutics

WHO Working Group on therapeutics

The Working Group meets regularly and has published two new meeting reports.

Current progress in the area of COVID 19 chemoprophylaxis.

Currently, there are no licensed vaccines for the prevention of COVID 19. While efforts continue to develop efficacious vaccines, it is pertinent to examine the possible role of therapeutic agents in protecting healthcare workers and the general populace who are at significant risk of contracting the virus, either before they are exposed to the virus or to prevent the development of clinical disease following exposure.

The Working Group met to 1. Review and critically appraise the existing evidence regarding promising therapeutics for chemoprophylaxis and 2. To decide on the best approach to evaluate the prophylactic and post-exposure prophylactic efficacy of the highlighted therapeutics. The Consultation represented an initial step towards the evaluation of available evidence and harmonization of ongoing scientific efforts.

Preliminary considerations were provided on a WHO generic protocol for the scientific evaluation of chemoprophylaxis in both pre and post exposure prophylaxis scenarios. A double-blind randomized placebo-controlled clinical trial is the encouraged methodology. Randomization could either be at the individual or household clusters or rings around an index case.

Four ongoing studies of chloroquine or hydroxychloroquine were presented. A large variability was observed in dosage, target population and trial design. WHO is working on a core protocol that could be ideally implemented in several countries with the main objective to protect Health Care Workers and limit nosocomial transmission.

WHO will convene another meeting to further deliberate on endpoints, the most ideal dose of chloroquine for the studies, and harmonization of protocols.

The meeting report is available at:
https://www.who.int/blueprint/priority-diseases/key-action/RD_Blueprint_expert_group_on_PEP_call_Mar_18_2020_MC.pdf?ua=1

Potential role of IL-6/IL-1 antagonists in the clinical management of COVID 19 infection

Some evidence suggests that a subgroup of patients with severe COVID-19 might have a "cytokine storm" syndrome. Current management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality. Data from China from severe patients show an increase of certain cytokines IL-2, IL-7, granulocyte-colony stimulating factor, interferon-γ, tumour necrosis factor-α and IL-6 suggesting that mortality might be due hyper pro-inflammatory immune reaction.

The Consultation represented an initial step towards the evaluation of IL-6 /IL-1 inhibitors to improve the severe cases of COVID-19. There are ongoing efforts to identify additional candidate therapeutics and to expand the body of evidence available on each of the candidates.

Interleukin 6 (IL-6) is a cytokine that plays an important role in immune response and is implicated in the pathogenesis in autoimmune diseases, multiple myeloma and prostate cancer. Tocilizumab is a monoclonal antibody against the interleukin-6 receptor (IL-6R), therefore an immunosuppressive therapy mainly for the treatment of rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis.

Clinically, the major human interleukin 1(IL-1) inhibitor is Anakinra, a recombinant modified version of IL-1 which binds to the IL-1 receptor and is used to treat rheumatoid arthritis. Rilonacept and Canakinumab bind directly to IL-1.

Given the very limited current evidence of the potential benefits of IL-6 inhibitors the WHO Working Group agreed to request a group of experts to prepare a background paper to describe the rational and justification for the inclusion of these therapies in a RCT. Therapeutic agents such as IL-6/IL-1 antagonists could have inadvertent adverse effects that need to be balanced against potential benefits in severe hospitalized patients by reducing the risks/effects of inflammatory reaction and the length of stay in ICUs. It was also noted that Tocilizumab has a very limited supply and is very expensive, therefore even it shows some benefit it may not be available for the treatment of large number of patients

The meeting report is available at:
https://www.who.int/blueprint/priority-diseases/key-action/Expert_group_IL6_IL1_call_25_mar2020.pdf?ua=1

Chloroquine and hydroxychloroquine

Large clinical trials are under way to generate the robust data needed to establish the efficacy and safety of chloroquine and hydroxychloroquine in the treatment of COVID-19. These medicines are currently authorised for malaria and certain autoimmune diseases and it is important that patients do not face shortages caused by stockpiling or use outside the authorised indications. Both chloroquine and hydroxychloroquine can have serious side effects, especially at high doses or when combined with other medicines.

Ahead of data being available from large clinical trials, some authorities, such as the US FDA, have judged that the potential benefits of widespread use of hydroxychloroquine and chloroquine outweigh the risks associated with the drugs. The FDA issued an Emergency Use Authorization (EUA) to allow hydroxychloroquine sulfate and chloroquine phosphate products donated to the Strategic National Stockpile(SNS) to be distributed and used for certain hospitalized patients with COVID-19. These drugs will be distributed from the SNS to states for doctors to prescribe to adolescent and adult patients hospitalized with COVID-19, as appropriate, when a clinical trial is not available or feasible.

Other authorities, such as the EMA, have issued advice that chloroquine and hydroxychloroquine are only to be used in clinical trials or emergency use programmes.
https://www.ema.europa.eu/en/news/covid-19-chloroquine-hydroxychloroquine-only-be-used-clinical-trials-emergency-use-programmes

ICMRA call on therapeutics and ongoing/planned trials

More than 25 NRAs joined a meeting organized by ICRMA on 2 April on therapeutics. Countries shared information on about 300 clinical trials in progress, the candidate therapeutics that are being studied, and identified common issues, problems and potential solutions. A report of the meeting will be available as soon as possible and more details can be shared in the next update.

Vaccines

Landscape of candidate vaccines for SARS-CoV-2

A landscape analysis of candidate SARS-CoV-2 vaccines is regularly published by WHO. The 26 March version is available at:
https://www.who.int/blueprint/priority-diseases/key-action/Novel_Coronavirus_Landscape_nCoV_Mar26.PDF?ua=1

The table gives a summary of the vaccine platforms under evaluation, and the NRAs involved in their assessment.

Stage of vaccine development	Type of platform	Number of vaccine candidates	NRA	Comments
Phase 1 clinical	Non-replicating viral vector	1	China	Ad 5 vector; trial in China
	RNA	1	USA	LNP-encapsulated mRNA; trial in USA
Pre-clinical	DNA	3	2 USA; 1 India	
	Inactivated whole virus	2	2 China	1 Alum adjuvanted
	Live attenuated	1	India	
	Non-replicating viral vector	7	4 USA 2 EMA 1 MHRA	6 adeno-based vectors; 1 vaccinia vector
	Protein subunit	18	8 USA 5 EMA 2 Canada 1 Australia 1 Israel 1 ?	8 spike protein; 10 other targets
	Replicating viral vector	6	3 USA 1 EMA 1 China 1 India	3 measles vectors; 1 horsepox; 1 influenza; 1 VSV
	RNA	7	3 China 2 USA 1 EMA 1 MHRA	4 mRNA; 2 LNP-encapsulated mRNA; 1 saRNA
	VLP	1	1 Canada	Plant-derived
	Unknown	7		

Plans to support accelerated access to candidate SARS-CoV-2 vaccines

WHO has considerable experience in preparing regulators for introduction of new vaccines. The experience with regulatory preparedness for pandemic influenza vaccines and with the recent ebola vaccine will be especially useful. AVAREF has agreed to activate their joint review process, at this stage for candidate therapeutics, but sensitizing African regulators to candidate vaccine, many of which are being developed using novel technologies, should start as soon as possible. Discussions with other regional regulatory networks are ongoing.

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

Convalescent plasma trials

WHO has used its convening powers to discuss the use of convalescent plasma with international organizations (EU, ECDC, CoE/EDQM) and with the International Society of Blood Transfusion ISBT (a Non-State Actor in official relations with WHO). WHO Regional Offices and Country Offices have provided information on convalescent plasma studies from national authorities and healthcare systems. Convalescent plasma studies (clinical trials and observational studies) have started or are about to start in China, USA, Saudi Arabia, Philippines and several countries of Europe. The information sharing led to a consensus on the importance of several criteria, such as

donor criteria, testing to ensure that a donor is free of the virus during donor selection, plasma collection by aphaeresis, antibody titer measurement of donations, and pathogen inactivation on convalescent plasma.

In at least one country, it is proving difficult to test the antibody titers of donations prior to pooling to prepare the convalescent plasma. Therefore, aliqouts of each donation and plasma pool are being stored so that they can be tested later. Outcomes from the treatment will be stratified in post-trial analyses to determine the effect of the titre of the convalescent plasma administered.

Several of these criteria might be difficult to implement in Low and Middle Income Countries (LMICs). The use of convalescent plasma for COVID-19 in these countries needs appropriate investigational and ethical consideration.

WHO will continue to liaise with its international partners to obtain and share information on countries conducting studies on Convalescent Plasma. In the EU, there is an upcoming EU programme of COVID-19 convalescent plasma collection and supply (including guidance on collection, testing, processing, storage, distribution and monitoring of outcome data).

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

Reports on progress with the WHO Working Groups will be provided in the next update.

Supply chain

Due to the issues outlined below LMICs in particular are having difficulties finding sources for core lists of medicines.

Travel restrictions and impact on shortages

With the travel restrictions and confinement procedures recently introduced in India, there has been a second wave of shortages of medicines and health products caused by transportation bottlenecks. In some countries, up to 75% of the health products that arrive via air freight are delivered in the cargo space of passenger flights, and the global flight disruptions have caused significant delays with products reaching their destinations, this includes FPPs, APIs and other products. Shipments delivered from UN, bi-lateral and UN, and civil society organizations moving to LMICs have been delayed as well. ICAO and WHO have both issued letters to broad audiences to propose mitigation strategies to address the problems this is causing.

Export restrictions

The number of countries imposing export restrictions on medicines and health products is increasing. Agencies have been in contact directly with government officials to request exemptions for certain products, which in some cases have been accepted. Overall, the restrictions are in part caused by speculative procurement and hoarding patterns. While the export restrictions in general are creating additional problems, there needs to be support to rationale buying to ensure that shortages do not re-emerge from spikes in demand that are speculative in nature.

Price increases/currency devaluations

While some companies have made commitments to not increase medicine prices as a result of the COVID19 outbreak, prices of medicines and weakening of financial markets are also contributing to difficulties for some countries in accessing medicines. For example, the recent devaluation and negative rating of the South African

Rand has substantially increased costs and problems with accessing medicines on the international markets, and shortages of HIV medicines are imminent.

Transportation cost increases

In addition to increases in the cost of medicines and health products, freight prices are also increasing drastically, adding significantly to the "landed cost" of needed supplies. In some cases, freight costs have increased 10-fold. While WHO acknowledges and applauds airlines that are repurposing their cancelled passenger flights (United, Lufthansa have made public statements to this affect), countries with limited financial resources will need significant assistance in obtaining medicines.

Quantification tools:

WHO has launched a new portal for COVID response. Within the portal activities are quantification tools for countries that need support in planning for surge needs.

https://www.who.int/emergencies/diseases/novel-coronavirus-2019

You have to click through "country support and technical guidance"

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance

and then to "operations support and logistics" which opens a page on a "disease commodity package", which is a list of devices and supplies.

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. Azithromycin, which was tested in combination with chloroquine and hydroxychloroquine, is one of the medicines currently at risk. Experimental medicines, including chloroquine and hydroxychloroquine remain subject to speculative buying and there are also reports of misuse as well as falsified and substandard products. WHO and other regulatory authorities have released guidance to promote improved use of these experimental products.

Paracetamol shortages continue; however, much of the initial shortage is theorized to have been related to consumer hoarding. It would be expected that the restrictions now in place for most pharmacies to ration sales to individuals will partially alleviate the shortage. However, WHO is continuing to monitor this product.

The problem with PPEs also continues around the world. The number of industrial entities that have converted their manufacturing capacity to produce PPEs is increasing, but the total capacity and throughput are somewhat unclear and when and if this will meet the demand. Compromised also by export restrictions, this area needs critical attention and planning to protect HCWs.

Falsified and substandard products

A rapid alert was published by WHO on 31 March on falsified medical products, including *in vitro* diagnostics, that claim to prevent, detect, treat or cure COVID-19. The alert is published in English, French and Spanish, and the other UN languages as soon as possible, and is available at:
https://www.who.int/docs/default-source/essential-medicines/drug-alerts20/no3-2020-falsified-mp-forcovid-en.pdf?sfvrsn=cd866001_8

WHO requests increased vigilance from national health authorities, healthcare professionals, members of the public and supply chain stakeholders worldwide to prevent the distribution of falsified medical products, including IVDs and laboratory reagents. Increased vigilance should focus on hospitals, clinics, health centres, clinical laboratories, wholesalers, distributors, pharmacies and any other suppliers of medical products. All medical products must be obtained from authentic and reliable sources. Their authenticity and condition of the product should be carefully checked. Consumers are advised to seek advice from a healthcare professional in case of doubt.

National health authorities are requested to immediately notify WHO if these falsified products are discovered in their country. If you have any information concerning the manufacture, distribution, or supply of these products, please contact rapidalert@who.int