Regulation of in vitro diagnostics, therapeutics, and vaccines
WHO Update – 11
Coronavirus disease 2019 (COVID-19)
05 June 2020

World Health Organization

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Key Messages

On 3 June WHO endorsed continuation of all arms of the Solidarity Trial, including hydroxychloroquine. WHO has stressed there is no current evidence of drugs that would effectively reduce mortality in COVID-19 patients. The only way to get the necessary evidence and definitive answers on potential therapeutics is through well-conducted randomized trials. WHO encourages researchers to continue carrying out trials and studies on different drugs to reduce the severity and mortality of the disease.

Highlights and main issues

- Regulators discussing digital transformation of regulatory processes, such as remote Good Clinical Practice audits, and evaluating potential benefits from its use during the ongoing pandemic
- WHO published Guidance for research ethics committees for rapid review of research during public health emergencies
- The Solidarity vaccine clinical trial protocol published by WHO – information sessions for regional regulators to be organized
- The Global Advisory Committee on Vaccine Safety (GACVS) met to identify challenges that are specific to vaccine safety monitoring, particularly in LMICs. Recommendations on the elements of a Pharmacovigilance (PV) preparedness workplan for Low- and Middle-income Countries (LMICs) ahead of COVID-19 vaccine roll-out and on the proposed approach and roadmap for COVID-19 vaccine risk/benefit communication were agreed
- A report at the WHO Animal Model Working Group (WG) showed that a neutralizing monoclonal antibody protected hACE2 transgenic mice against lower respiratory infection when the mice were challenged with SARS-CoV-2 one day after intraperitoneal administration of the antibody
- The COVID-19 technology access pool launched on 29th May
- ACT accelerator work on vaccines, diagnostics, therapeutics and health systems intensifies
- Expression of Interest for emergency use listing of antigen detection assays expected to be launched by 10 June 2020

COVID-19 technology access pool (C-TAP) activated

First proposed by the President Carlos Alvarado of Costa Rica, the COVID-19 Technology Access Pool (C-TAP) was officially launched on 29 May, aimed at making vaccines, tests, treatments and other health technologies to fight COVID-19 accessible to all. To date thirty countries and multiple international partners and institutions have signed up to support the initiative.

The top 5 priorities for C-TAP are:

1. Public disclosure of gene sequences and data
2. Transparency around the publication of all clinical trial results
3. Governments and other funders are encouraged to include clauses in funding agreements with pharmaceutical companies and other innovators about equitable distribution, affordability and the publication of trial data
4. Licensing any potential treatment, diagnostic, vaccine or other health technology to the Medicines Patent Pool
5. Promotion of open innovation models and technology transfer that increase local manufacturing and supply capacity, including through joining the Open COVID Pledge and the Technology Access Partnership (TAP)

Alignment of approaches by regulatory groups

Global regulators work towards alignment on policy approaches and regulatory flexibility during COVID-19

As part of its coordinated response to the pandemic, the International Coalition of Medicines Regulatory Authorities (ICMRA) convened its regular high-level meeting of regulators from around the world on 27 May 2020 to discuss COVID-19 policies, regulatory aspects of COVID-19 medicine development and pragmatic approaches to address challenges posed by the ongoing pandemic. The ICMRA COVID-19 Working Group, chaired by Health Canada, is composed of several delegates from the ICMRA membership, including WHO. The working group will initially work on regulatory criteria for the prioritisation of COVID-19 vaccines; guidance on the prioritisation of clinical trials; and the coordination of trial registries.

Participants of the 27 May meeting exchanged information about the growing number of medicines that are in development or in clinical trials to assess their safety and efficacy for the treatment or prevention of COVID-19. They noted that clinical trials must be adequately powered, well-designed and include a control arm with standard of care (i.e. standard treatment) to generate evidence upon which decisions can be based. It was highlighted that, as new information is produced continuously, there is the risk for trials to be discontinued early without producing the necessary evidence and knowledge. Participants recommended that, provided the safety of trial participants is ensured, clinical trials should not be prematurely discontinued. They acknowledged the importance of striking a balance between speed and safety by supporting the rapid development of COVID-19 treatments but also insisting on the generation of robust data to demonstrate their safety and efficacy and enable decision-making.

Global regulators have implemented flexible and pragmatic approaches to ensure continuity of medicine supply and oversight and to also protect public health in light of the medical emergency presented by COVID-19. For instance, European Medicines Agency (EMA) has applied extraordinary measures in different areas of medicine regulation, such as inspections of manufacturing facilities, pharmacovigilance corrective and preventive action plans, audits and the validity of good manufacturing practice (GMP) certificates.

Guidance for remote good clinical practice (GCP) inspections is being developed in the EU. Other regulators also shared insights into virtual evaluations and remote GCP inspections. Meeting participants agreed that these measures have benefited from digital transformation of regulatory processes during the ongoing pandemic. They concluded that convergence in rolling back exceptional regulatory flexibilities after the crisis and a comprehensive assessment of possible benefits of some of these adaptations in different countries would be critical.

ICMRA Update #3 (27 May 2020)

The ICMRA meeting report – Update #3 (28 May 2020)

Global regulators commit to cooperate on observational research in the context of COVID-19

As reported in the 10th WHO Regulatory update, regulators from around the world agreed in a meeting convened by ICMRA on 19 May three priority areas for cooperation on observational research during COVID-19. They agreed to step up their cooperation in the following three areas:

- **Pregnancy research** to examine the impact of both coronavirus disease and medication use on pregnant women infected with SARS-CoV-2 and on their unborn babies in order to support COVID-19 medicine development, risk management, and planning for safety monitoring of vaccines and therapeutics;
- **Building international clinical cohorts of COVID-19 patients** to share expertise and increase study power and data quality in order to meet regulatory requirements and address existing knowledge gaps; and
- **Prepare strong infrastructure for monitoring the safety and effectiveness of vaccines** against COVID-19 in order to rapidly detect and minimise risks to patients.

The ICMRA meeting News on Observational research in the context of COVID-19 (19 May 2020)

The ICMRA meeting Summary Report on COVID-19 Real-World Evidence and Observational studies (19 May 2020)

African Vaccines Regulatory Forum (AVAREF)

A series of webinars for regulators and ethics committees were organized by the AVAREF Secretariat aiming to build ethics and regulatory capacity and to provide guidance for timely reviews and approval of clinical trial applications and their oversight towards accelerated development of priority medical products against COVID-19.

So far four webinars have been held as outlined:

1. Basic Virology and Targets for Vaccines and Therapeutics, 14 May 2020.
2. AVAREF Joint Review Process – Digital Survey Findings, 21 May 2020
3. AVAREF COVID Expedited Review Process, 28 May 2020.
4. DAC (Design, Analyze, Communicate): A tool for efficient protocol review for Ethics Committees and Regulators, 4 June 2020

The Webinars provided the opportunity to improve the knowledge of the ethics committees and regulators on basic virology, SARS-COV-2, vaccines and therapeutics targets, candidates and to discuss AVAREF joint review procedure, its endorsed emergency expedited clinical trial review guidance for its joint review procedure and efficient review of CT protocols.

For more information on AVAREF Webinars, please contact Professor Bartholomew Dicky Akanmori at akanmorib@who.int

Regulatory update meetings for the Americas

Bi-weekly meetings for the regulators of the Americas are being convened by PAHO in English and Spanish. In the 28 May meeting, WHO shared a global regulatory update to improve access to vaccines, therapeutics, diagnostics, and medical devices for COVID-19. Topics discussed included the ACT accelerator, new IVDs available through PQ Emergency Use Listing (EUL), vaccine initiatives, the Solidarity clinical trial, Substandard and Falsified products, and joint initiatives from regulators on regulatory flexibility and promoting reliance.

WHO presentation and links to further materials are available at PRAIS : PAHO's COVID-19 community of practice

For those who have not yet registered: Registration to PRAIS

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.

46 submissions for NAT assays have been received so far.

The status of each application is presented here (02 June)

Ten 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
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.
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 5 June 2020 WHO listed the following NAT assay under the emergency use listing procedure:

- The SARS-CoV-2 Nucleic Acid Test (Real-time PCR) **manufactured by Shanghai Kehua Bio-engineering Co., Ltd.** is an in vitro diagnostic test for the qualitative detection of nucleic acid from the SARS-CoV-2 in nasopharyngeal specimens. The assay should be used in combination with the nucleic acid extraction product of Shanghai Kehua bio-engineering Co., Ltd and the fluorescent real-time PCR instruments with at least four detection channels (FAM, VIC /HEX, ROX/TEXAS RED, Cy5) such as ABI7500, Bio-Rad CFX96, Tianlong Gentier 96E, etc.

Antibody detection rapid tests have been eligible for WHO emergency use assessment since 17 April. WHO received four expressions of interest for antibody detection RDTs and several pre-submission calls have been held with manufacturers interested in submitting for EUL assessment.

WHO has well advanced the development of instructions for submission of antibody detection enzyme immunoassays (EIAs) and antigen detection RDTs. The instructions for submission of antigen detection assays will be posted on the WHO website by 10 June 2020.

NIBSC collaborative study to establish a WHO International Standard for SARS-CoV-2 RNA

The aim of the collaborative study coordinated by the WHO collaborative centre NIBSC is to evaluate candidate preparations to act as 1st WHO International Standard for SARS-CoV-2 RNA, and harmonise results for nucleic acid based technology assay for the detection of SARS-CoV-2 between different labs and different methods, increasing comparability among studies.

The collaborative study is scheduled to start at the beginning of July. All NAT assays listed under the WHO EUL procedure will be involved in the collaborative study.

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 (02 June)

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.

Guidance for research ethics committees for rapid review of research during public health emergencies

Conducting research on new medications or vaccines during a pandemic is essential, and research ethics committees need to be prepared to rapidly review related research projects. WHO has published brief guidance that includes recommendations for changes to existing standard operating procedures in order to facilitate time-sensitive ethics review.

28 May 2020	Ethical considerations to guide the use of digital proximity tracking technologies for COVID-19 contact tracing
28 May 2020	Guidance for research ethics committees for rapid review of research during public health emergencies
3 May 2020	Key criteria for the ethical acceptability of COVID-19 human challenge studies

	WHO Working Group for Guidance on Human Challenge Studies in COVID-19 (vaccines)
20 Apr 2020	Q&A: Ethics and COVID-19: resource allocation and priority setting
25 Mar 2020	Ethical standards for research during public health emergencies: Distilling existing guidance to support COVID-19 R&D

Online training courses

Therapeutics

WHO endorses continuation of all arms of the Solidarity Trial, including hydroxychloroquine

On 3 June WHO endorsed continuation of all arms of the Solidarity Trial, including hydroxychloroquine.

As reported in an addendum to Regulatory Update 10 (26 May), the Executive Group of the Solidarity Trial sent a letter on 24 May to all National Principal Investigators informing them of a decision to implement a temporary suspension of random allocation to the hydroxychloroquine (HCQ) arm of the trial. This was in response to an observational study on hydroxychloroquine and chloroquine and its effects on COVID-19 patients that have been hospitalized published by the Lancet. The Solidarity Data Safety Monitoring Board were requested to undertake an extensive review data from the Solidarity Trial and other ongoing trials, as well as any evidence published so far to inform a final decision whether or not to continue with the HCQ arm.

After the Data Safety and Monitoring Committee of the Solidarity Trial reviewed the data, including the available mortality data, they recommended that there are no reasons to modify the trial protocol and the Executive Group endorsed the continuation of all arms of the Solidarity Trial, including hydroxychloroquine.

WHO has stressed there is no current evidence of drugs that would effectively reduce mortality in COVID-19 patients. The only way to get the necessary evidence and definitive answers on potential therapeutics is through well-conducted randomized trials, and this is why WHO encourages researchers to continue carrying out trials and studies on different drugs to reduce the severity and mortality of the disease.

WHO hopes that the ongoing trials will continue gathering further evidence on the efficacy of HCQ.

Safety and efficacy of hydroxychloroquine or chloroquine for treatment of COVID-19

A targeted update, which includes data from Randomized controlled trials (RCTs) and quasi-experimental studies comparing the use of hydroxychloroquine or chloroquine (with or without a macrolide) with standard care as a treatment for COVID-19, was posted by WHO on 29 May. The protocol and data for the targeted updated comes from the COVID-NMA project led by Cochrane France in collaboration with Cochrane Germany, Cochrane Ireland, the Centre for Evidence-Based Medicine Odense, and the Centre of Research Epidemiology and Statistics (Université de Paris, Inserm). The WHO International Clinical Trials Registry Platform and electronic bibliographic databases (PubMed, MedRχiv, Chinaxiv) were searched. Systematic review and meta-analyses of COVID-19 treatments were retrieved and the references screened. No language restrictions were used. The report is based on searches conducted up to and including May 23, 2020.

The main conclusions were that hydroxychloroquine and chloroquine were not associated with a difference in overall mortality when compared to standard care for COVID-19 but may result in a shorter time to intubation, death, and ventricular arrythmia.

Targeted Update: Safety and efficacy of hydroxychloroquine or chloroquine for treatment of COVID-19 (29 May)

Hydroxychloroquine or chloroquine clinical trials/study arms for COVID-19 prophylaxis and post-exposure prophylaxis

The WHO Therapeutics Working Group met on 28 May to discuss implications for ongoing prophylaxis (PrEP) and post-exposure prophylaxis (PEP) studies of the temporary suspension by WHO of enrollment of patients into the hydroxychloroquine (HCQ) arm of the Solidarity Trial. The scientific rationale for continuation is that PrEP and PEP studies are testing lower doses of HCQ or CQ than treatment studies.

Regulatory authorities in South Africa, the EU, and the USA have not halted enrolment in PrEP and/or PEP studies, whereas the MHRA in the UK has done so. All principal investigators of PrEP and/or PEP studies who attended the meeting reported a negative impact on enrolment in ongoing studies due to publicity surrounding the recent Lancet paper, and a particularly marked negative impact when the WHO announced that the HCQ arm of Solidarity was being 'temporarily suspended'.

There was consensus in the meeting that the ongoing randomized controlled PrEP and PEP trials of HCQ and CQ in health care workers, and in family members of people known to be COVID positive, should continue. Such studies will provide the most rapid highest quality evidence of the risks and benefits of the use of HCQ and CQ for prophylaxis or post-exposure prophylaxis.

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 update (summarised in WHO Regulatory Update No. 10), 635 new case reports have been reported to VigiBase, the WHO Global database of Individual Case Safety Reports. Most of these describe at least one drug or substance included in the WHO Solidarity trial (i.e. hydroxychloroquine or chloroquine), azithromycin, the combination lopinavir/ritonavir and remdesivir) as either suspected or interacting.

A smaller number of the reports describe other drugs, not included in the WHO Solidarity Trials, but known to be used in the treatment of COVID-19 disease. Among these, tocilizumab is the most reported (over 100 reports).

The reported adverse reactions 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 is the concomitant use of multiple interacting medications; for example, there are several reports in this review that detail an interaction between lopinavir/ritonavir and direct oral anticoagulants (DOAC). The serious events identified in previous reviews, including DRESS (Drug Rash with Eosinophilia and Systemic Symptom), completed suicide and sudden death remain under surveillance.

A descriptive analysis of the new reports (02 June)

Vaccines

Solidarity vaccine clinical trial protocol

This large, international, randomized controlled clinical trial is designed to enable an expeditious, agile and concurrent evaluation of the benefits and risks of multiple candidate preventive vaccines against COVID-19 at international sites with sufficient COVID-19 attack rates. Different candidate vaccines may be available or suitable to enter the trial at different times; for each candidate vaccine, the primary efficacy results are expected within 3-6 months of the vaccine entering the trial.

The trial will rapidly enrol and individually randomize very large numbers of adult participants in many different populations. Each participant will be contacted weekly for information as to whether any potentially relevant symptoms have arisen, with laboratory testing triggered if the report suggests COVID-19. By using a shared placebo/control group and a common Core protocol to evaluate multiple candidate vaccines in the trial, resources allocated to the evaluation of each candidate vaccine are judiciously saved while a high standard of scientific rigor and efficiency is ensured.

The trial is designed to provide sufficient evidence of safety and vaccine efficacy against COVID-19 to support decision-making about global vaccine deployment, which may include licensure and/or WHO pre-qualification.

Final decisions about COVID-19 vaccine deployment will be made in each jurisdiction.

The WHO R&D Blueprint team in collaboration with the WHO Regulation and Prequalification team will be organising regional information sessions for regulators in the coming weeks.

> Solidarity vaccine clinical trial protocol: An international randomised trial of candidate vaccines against COVID-19

Global Advisory Committee on Vaccine Safety (GACVS)

The GACVS met virtually on 27 and 28 May 2020, focused on safety preparedness around COVID-19 vaccine deployment. Acknowledging the unprecedented short timeframe for COVID-19 vaccine development, it is likely that limited safety data will be available at the time of deployment. Consequently, more effort will be required by implementing countries on safety monitoring, in settings that are likely be overburdened by the pandemic.

The population targeted by the COVID-19 vaccine will differ from the usual scope of immunization programmes, and hence the launch will require dedicated strategies. Large-scale deployment is expected, over a short period of time. Timely detection and management of safety concerns would be critical, to retain trust in the immunization programmes and on public health authorities. In this context, GACVS has a critical role to play in guiding countries on preparing for the potential introduction of COVID-19 vaccines.

The objectives of the meeting were to:

1. Identify challenges that are specific to vaccine safety monitoring, particularly in LMICs, related to the:
    a. Surveillance platforms and processes that are unique to pandemic or epidemic situations, and
    b. Specific AEFIs and detection of signals
2. Determine systems and capacity that would be required, particularly in LMICs, to monitor, assess and manage known and unknown AEFI in the context of COVID-19 vaccines
3. Review and provide recommendations on the elements of a PV preparedness workplan for LMICs ahead of COVID-19 vaccine roll-out
4. Review and provide recommendations on the proposed approach and roadmap for COVID-19

vaccine risk/benefit communication

A full report of the conclusions and recommendations from the meeting will be published in the Weekly Epidemiological Record on 13 July 2020.

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 June)

Convalescent plasma

On 27 May 2020, the Blood and other Products of Human Origin (BTT) team of the Technical Standards and Specifications (TSS) Unit in the Department of Health Products Policy and Standard at WHO Headquarters conducted two sessions of Webinar on "Maintaining blood supply and safety and collecting convalescent plasma during the COVID-19 pandemic: WHO perspectives and actions in blood establishments".

The Webinar aimed to raise awareness that blood supply and safety are to be ensured, even during an emergency situation such as the current COVID-19 pandemic. Moreover, collection and use of COVID-19 Convalescent Plasma (CP) was also presented to address the current situation where more and more countries are conducting clinical trials on COVID-19 CP as a potential treatment.

Nearly 400 people including WHO Regional and Country Offices, blood establishments, international blood related organizations, patient`s organizations and people who interested in blood services attended the Webinar .

Webinar materials: Maintaining blood supply and safety and collecting convalescent plasma during the COVID-19 pandemic: WHO perspectives and actions in blood establishments

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

WHO Working Group on Assays and Reference Preparations

Discussion in the WG on Assay and Reference Preparations on 27 May 2020 was focused on (a) the T cell response and (b) systems serology. In the context of T cell response, the need for a cytokine agnostic approach was considered important in order to cover most aspects of the immune response.

A study was presented that showed a correlation between the antibody response and $CD4^+$ response for samples taken during the convalescent phase of COVID-19 infection. However, it was reported that 50% of unexposed subjects had a $CD4^+$ response but pre-existing antibodies were not detected. This was not possible to explain but indicates a need for further investigations. In particular, testing for pre-existing immunity in phase I and II clinical trials will be critical for the interpretation of results.

A systems serology study in non-human primates was presented which showed a robust IgG1 response and neutralization titres associated with the peaks of viremia. The importance of other qualities of antibodies (i.e., phagocytic and complement functions) that could serve as indicators or predictors of protection in addition to the neutralization titres was emphasized.

The 3 June meeting discussed a newly established global working group on coronavirus assay standards. The aims of the US-led group are to develop guidance on assay standards and to conduct collaborative studies to validate assay reference and assay control preparations. The group had identified more than 50 such materials that are commercially available currently. The attributes of these materials are described in differing ways and one ambition of the group is to develop a minimal information standard so that reference and control preparation attributes can be described in a standard way. The group is also considering setting up collaborative studies to compare the reference and control preparations.

The Working Group strongly advised that this should be done in coordination with WHO. The proposed collaborative study would be very useful if used to calibrate the existing reference and control materials against a WHO International Standard.

In an update on development of WHO International Standards, NIBSC, a WHO Collaborating Centre, reported that the collaborative study to validate the candidate standards would begin in July, with results expected in August. So far about 50 laboratories had indicated their intent to participate in the study.

WHO Working Group on Animal Models

In the 27 May meeting, updates on pathogenesis studies of SARS-CoV-2 in hACE2 transgenic mice and hamsters were presented. Experiments were also reported of passive immunization with a neutralizing IgG1 monoclonal antibody identified by phage/yeast display. Similar neutralizing antibodies have been evaluated as therapeutics for MERS, Hendra and Nipah virus infections.

The monoclonal antibody protected hACE2 transgenic mice against lower respiratory infection when the mice were challenged with SARS-CoV-2 one day after intraperitoneal administration of the antibody. The antibody did not enhance SARS-CoV-2 pseudovirus entry in a cell-culture system. The developers consider the monoclonal antibody is promising for prevention and therapy of COVID-19 and plan to evaluate it in humans.

In the 4 June meeting, several groups reported that pigs were not susceptible to infection with SARS-CoV-2. On the other hand, ferrets are susceptible and a detailed description of the pathogenesis of SARS-CoV-2 in ferrets, funded by US FDA, was presented. Infection in ferrets is clinically mild with peak virus titers in nasal swabs on days 2-4 after challenge and bronchial pneumonia occurs. A neutralizing antibody response occurs from day 8 onwards. Animals that had been infected and allowed to recovery were protected against lower respiratory tract infection on re-challenge, but virus was detected in the upper respiratory tract. This is consistent with findings reported from non-human primates.

Substandard and Falsified products

In response to the first report of a falsified Covid19 vaccine, WHO is preparing for detailed inquiries.

Update on Alert n4/2020 (falsified chloroquine) has been published with photographs of target products.

Update on Alert n4/2020

Supply chain updates from WHO HQ and Reginal Offices

Shipments from UN partners:

Shipments to countries continue from the UN supply chain consortium, including over 100 shipments to countries in WHO regions; some supplies, particularly gowns, remain in limited supply. Note that medicines

for use in eligible clinical trials are not included and should be referred to teams managing the Solidarity Trials. Quantification tools are being translated into other WHO languages to facilitate use.

Despite ongoing difficulties with supply chain disruptions, WHO has so far managed to purchase and ship millions of items of PPE to 133 countries, and diagnostic kits to 126 countries. However, more still needs to be done to get life-shaping shipments to places around the world where COVID-19 has hit the hardest.

Requesting and receiving supplies

COVID-19 Partners Platform & Supply Portal

COVID-19 Supply Chain System process flow (18 May)

Shortages:

WHO continues to monitor shortages across regional networks, industry associations and regulatory networks. Supply of propofol and other anesthetics has improved along with most ICU medicines, however, isolated problems with export restrictions are still impacting paracetamol. While acute shortages have decreased, there are still supply constraints for some products, including diagnostics.

As demand for non-COVID services are beginning to resume, there have been reports of shortages of medicines for malaria and HIV as well as some countries reporting shortages of insulin.

As additional monitoring and preparedness activities move forward, guidance for rapid supply assessments are being developed to support facility and national level preparedness. The guidance is overarching and includes supply chain information and rapid assessments of shortages. Tools will be developed to accompany the guidance document.

Operational guidance for the COVID-19 context (01 June)

The following medicines remain in constrained supply:

- 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) note: problems with API are the cause of the constraints with the latter two products.
- HIV: Lopinavir/ritonavir
- NCD: Metformin and insulin

Other products remaining constrained:

- *Blood and plasma*
- *PPE*
- *Oxygen and ventilators.*

Medical Devices

Personal protective equipment and community masks

WHO is leading a technical advisory group for personal protective equipment and community masks, with 3 groups:

Group 1: Standards and technical specifications, QA, database of approved products

Group 2: Local Production, re-use-innovation

Group 3: Prioritization, use, allocation, equity

Representation from regulatory agencies, especially from WPRO, SEARO, AFRO would be very welcome, and experts are requested to indicate their interest at covid_med_devices@who.int

African Medical Devices Forum (AMDF)

African Medical Devices Forum (AMDF) with the support of the Africa Medicines Regulatory Harmonization (AMRH) Joint secretariat (WHO and AUDA-NEPAD) is organizing a Webinar for African Union (AU) Member States National Regulatory Authorities (NRA) on 10th June 2020 titled "Regulation of in-vitro diagnostics and medical devices in Africa: The role of NRAs". Objectives of this webinar are:

a. To familiarize AU Member States NRAs on the list of assays, medical devices and PPEs and guidance documents developed by the AMDF as an AMRH Technical Committee; and
b. To share global updates and experiences on regulatory response to Covid-19.

The information expected to be discussed with NRAs during the webinar will be available for AU NRA experts on MedNet platform.

Report of Africa Medical Devices Forum COVID-19 Task Force (available also in French)

WHO's country and technical guidance on COVID-19

Technical guidance Hub on COVID-19

Country preparedness and response status for COVID-19 (01 June)

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