Regulation of in vitro diagnostics, therapeutics, and vaccines
WHO Update – 12
Coronavirus disease 2019 (COVID-19)
19 June 2020

World Health Organization

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Key Messages

WHO welcomes the initial clinical trial results from the UK that show dexamethasone, a corticosteroid, can be lifesaving for patients who are critically ill with COVID-19. The findings reinforce the importance of large randomized control trials that produce actionable evidence. WHO will coordinate a meta-analysis to increase our overall understanding of this intervention. WHO clinical guidance will be updated to reflect how and when the drug should be used in COVID-19.

Highlights and main issues

- On 17 June 2020, WHO announced that the hydroxychloroquine (HCQ) arm of the Solidarity Trial to find an effective COVID-19 treatment was being stopped. The trial's Executive Group and principal investigators made the decision based on evidence from the Solidarity Trial, UK's Recovery trial and a Cochrane review of other evidence on hydroxychloroquine.
- Registration is open until 25 June for a Global Research and Innovation Forum on COVID-19. This will be a virtual event that will take place over two days on 1-2 July 2020 from 13h00 to 15h30 CET.
- The scope of the WHO EUL for SARS-CoV-2 virus IVDs has been expanded to antigen detection RDTs.
- A WHO convened Advisory Group has published a report on the feasibility, potential value and limitations of establishing a closely monitored challenge model of experimental SARS-CoV-2 infection and illness in healthy young adult volunteers. The report is available for comment until 23 June.
- A survey of global animal laboratories capacities to support vaccine and therapeutic evaluation has been published by WHO.
- National governments, local UN offices and civil society procurers who are purchasing PPEs, equipment and diagnostics from some national markets have reported challenges with local capacity to perform sufficient quality assurance reviews of the products. WHO is considering options to support these procurers in collaboration with its regional and country offices.

Virtual Global Research and Innovation Forum on COVID-19

The Global Research and Innovation Forum on COVID-19 will be a virtual event that will take place on **1st and 2nd July 2020** from **13h00 to 15h30 CET**. The meeting is a follow up to the face to face Forum held in February 2020 in WHO headquarters in Geneva, Switzerland and will mainly focus on:

DAY 1: 1st July

1. **CRITICAL RESEARCH FINDINGS** and their **IMPACT** on the response to COVID-19
2. **PROGRESS** with the implementation of the Global Research Roadmap

DAY2: 2nd July

3. **EMERGING RESEARCH QUESTIONS** and the science gaps
4. **NEW RESEARCH PRIORITIES** for the Global Research Roadmap

The following research topics will be addressed:

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

To indicate your interest in participating, please register by **25 June 2020**. Please note that during the registration, you will be prompted to indicate your focus areas of research on Covid-19, any pertinent publications to highlight, and contributions to advancing the goals of the Global Research Roadmap.

Participation is especially encouraged from Asia and Africa as these were under represented in the February meeting.

Registration (please ensure to use Chrome as web browser for registration)

Alignment of approaches by regulatory groups

Considerations for Regulatory Oversight of Clinical Trials in the COVID-19 Pandemic

The 8th Regulatory Update meeting with the regulators in the Americas, convened by AMRO/PAHO on 18 June, discussed new guidance from AMRO/PAHO on "Considerations for Regulatory Oversight of Clinical Trials in the COVID-19 Pandemic". Continental models and efficiencies in a pandemic for clinical trials regulation based on the African Vaccines Regulatory Forum (AVAREF) was presented and discussed.

It was emphasized that efficiency gains achieved in the joint review of a Clinical Trial Authorization could be negated by lengthy post-authorization steps required for the start of the trial to begin. The challenges regulatory authorities face in conducting clinical trial (CT) oversight during the COVID pandemic, and best

practices/ lessons learned, were then discussed by participants. Remote review methodologies for CTs have been introduced in several countries of the Americas.

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

The International Coalition of Medicine Regulatory Authorities (ICMRA) convened its regular virtual meeting of regulators from around the world on 12 June 2020 to discuss high-level policy issues and regulatory approaches to ensure a coordinated response to the ongoing COVID-19 pandemic.

Meeting participants discussed the progress made on the development of ICMRA guiding principles for COVID-19 clinical trials and prioritisation of compounds. They agreed that a clear distinction between exploratory clinical trials and confirmatory studies with investigational or repurposed medicines for the treatment of COVID-19 is critical for clinical trial prioritisation. Regulators also shared concerns about the discontinuation of clinical trials globally and the growing number of underpowered studies that might not generate the robust data required for regulatory decision-making.

All ICMRA members stressed the need for continuation of COVID-19 clinical trials that might produce conclusive evidence on the effects of potential treatments and vaccines against COVID-19, provided that the safety of trial participants is ensured. They reiterated that the research community should pool resources into large, well-designed, randomised clinical trials to determine which investigational or repurposed medicines would be safe and effective for the treatment or prevention of COVID-19.

In addition, participants in the high-level meeting discussed the use of COVID-19 clinical trial master protocols around the world to accelerate the development and approval of potential treatments and vaccines against COVID-19. ICMRA members are currently working on a list of ongoing and planned COVID- 19 clinical trials with master protocols in different countries and regions in order to compare the protocols and identify possible overlaps, for example regarding objectives and types of investigational agents studied. Regulators aim to update this list on a regular basis.

The ICMRA Working Group on COVID-19 also provided meeting participants with an update on its activities related to COVID-19 clinical trials, potential therapeutics and vaccines. Topics under discussion include ethical questions around human challenge trials and post-approval requirements for COVID-19 vaccines.

ICMRA members agreed to analyse the regulatory flexibilities and extraordinary measures applied in different areas during the pandemic in order to identify practices that should be maintained or stopped after the public health emergency. The ICMRA COVID-19 Working Group will keep updating all ICMRA members on the progress of these initiatives.

ICMRA WG meeting report - update #4 15 June 2020

In vitro diagnostics

WHO EUL for SARS-CoV-2 virus IVDs: scope expanded to antigen detection RDTs

The WHO Prequalification Unit is assessing products for Emergency Use Listing (EUL) for candidate in vitro diagnostics (IVDs) to detect SARS-CoV-2. Currently, the following IVDs are eligible for EUL submission:

- Assays for the detection of SARS-CoV-2 nucleic acid;
- Rapid diagnostic tests for the detection of IgM/IgG to SARS-CoV-2; and
- Rapid diagnostic tests for the detection of SARS-CoV-2 antigens.

Applicants submit their applications for assessment based on WHO instructions for NAT and rapid diagnostics tests detecting SARS-CoV-2 antigens (09 June 2020) and antibody detection rapid tests (RDTs) submissions.

47 expressions of interest for NAT assays, 7 for antibody detection RDTs and several pre-submission calls have been held with manufacturers interested in submitting for EUL assessment.

The status of each application is presented here (16 June 2020)

Manufacturers interested in the EUL submission are invited to contact WHO at diagnostics@who.int and schedule a pre-submission call.

Twelve 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
15 June 2020	COVID-19 Real-Time PCR Kit	HBRT-COVID-19	Chaozhaou Hybribio Biochemistry Ltd.
11 June 2020	Novel Coronavirus 2019-nCoV Nucleic Acid Detection Kit (Real Time PCR)	GZ-D2RM25	Shanghai GeneoDx Biotechnology Co., Ltd
5 June 2020	SARS-CoV-2 Nucleic Acid Test (Real-time PCR)	KH-G-M-574-48	Shanghai Kehua Bio-engineering Co., Ltd
22 May 2020	Novel Coronavirus (SARS-CoV-2) Real Time Multiplex RT-PCR Kit	RR-0485-02	Shanghai ZJ Bio-Tech Co., Ltd
21 May 2020	FTD SARS-CoV-2	11416300	Fast Track Diagnostics Luxembourg S.à.r.l.
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 11 and 15 June 2020 respectively, WHO listed the following NAT assays under the emergency use listing procedure:

- The **Novel Coronavirus 2019-nCoV Nucleic Acid Detection Kit (Real Time PCR)** manufactured by **Shanghai GeneoDx Biotechnology Co., Ltd** is used for *in vitro* qualitative detection of the ORF1ab and N genes of SARS-CoV-2 RNA in nasopharyngeal swabs and sputum specimens of suspected pneumonia cases, suspected cluster cases infected by novel coronavirus, and other patients requiring diagnosis or differential diagnosis of the novel coronavirus infection. The 2019-nCoV detection kit is automated and intended for use with GenAct NE-48 or QIAamp Viral RNA Mini Kit for Extraction/Purification and ABI7500 Instrument for amplification and detection.

- The **COVID-19 Real-Time PCR Kit** manufactured by **Chaozhaou Hybribio Biochemistry Ltd.** is designed for the qualitative detection of nucleic acids from SARS-CoV-2 oropharyngeal swab and nasopharyngeal swab specimens from patients who meet COVID-19 clinical and/or epidemiological criteria. The kit is intended for use with the Thermofisher Kingfisher Flex / Bioer GenePure Pro Nucleic Acid Purification System with related extraction kits and the Applied Biosystems Real time PCR system 7500 with software v2.0.5. / Bio-Rad CFX96 Real-Time PCR Detection System with Software / SLAN 96S RealTime PCR System with Software.

NIBSC collaborative study to establish the 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 (16 June 2020)

Note: WHO does not endorse any of the lists provided by NRAs. The information is provided exclusively to assist stakeholders with identifying the links to the various lists.

"Solidarity II" global serologic study for COVID-19

A complete understanding of the epidemiology and global risk posed by SARS-CoV-2 requires systematic serologic testing. Solidarity II is a global collaboration led by WHO that promotes the implementation of serological surveys of SARS-CoV-2, providing a collaborative environment for public health agencies and academic institutions around the world to work together to answer some of the most urgent questions about the COVID-19 pandemic.

Understanding the occurrence of infection with SARS-CoV-2 infection is critical for the world to know how frequently infection occurs among different populations, how many people have had mild or asymptomatically infection, how many people have been infected but may not have been identified by routine disease surveillance, and what proportion of the population may be immune from infection by SARS-CoV-2 in the future.

Unique features of Solidarity II are that it provides a global platform for government and academic collaborators to share cutting-edge scientific advances in the area of serologic surveys; accelerates progress globally towards understanding the COVID-19 pandemic; provides every country access to the tools and procedures needed to conduct their own serologic surveys; and promotes access to scientific discovery for all populations globally.

Information about "Solidarity II" Global Serologic Study for COVID-19

Therapeutics

WHO welcomes the initial clinical trial results from the UK on dexamethasone

WHO welcomes the initial clinical trial results from the UK that show dexamethasone, a corticosteroid, can be lifesaving for patients who are critically ill with COVID-19. For patients on ventilators, the treatment was shown to reduce mortality by about one third, and for patients requiring only oxygen, mortality was cut by about one fifth, according to preliminary findings shared with WHO. The benefit was only seen in patients seriously ill with COVID-19 and was not observed in patients with milder disease.

Dexamethasone is a steroid that has been used since the 1960s to reduce inflammation in a range of conditions, including inflammatory disorders and certain cancers. It has been listed on the WHO Model List of Essential Medicines since 1977 in multiple formulations and is currently off-patent and affordably available in most countries.

The researchers shared initial insights about the results of the trial with WHO, and we are looking forward to the full data analysis in the coming days. WHO will coordinate a meta-analysis to increase our overall understanding of this intervention. WHO clinical guidance will be updated to reflect how and when the drug should be used in COVID-19.

The findings reinforce the importance of large randomized control trials that produce actionable evidence. WHO will continue to work together with all partners to further develop lifesaving therapeutics and vaccines to tackle COVID-19 including under the umbrella of the Access to COVID-19 Tools Accelerator.

The hydroxychloroquine (HCQ) arm of the Solidarity Trial to find an effective COVID-19 treatment has been stopped

On 17 June 2020, WHO announced that the hydroxychloroquine (HCQ) arm of the Solidarity Trial to find an effective COVID-19 treatment was being stopped. The trial's Executive Group and principal investigators made the decision based on evidence from the Solidarity Trial, UK's Recovery trial and a Cochrane review of other evidence on hydroxychloroquine.

Data from Solidarity (including the French Discovery trial data) and the recently announced results from the UKs Recovery trial both showed that hydroxychloroquine does not result in the reduction of mortality of hospitalised COVID-19 patients, when compared with standard of care. Investigators will not randomize further patients to hydroxychloroquine in the Solidarity trial. Patients who have already started hydroxychloroquine but who have not yet finished their course in the trial may complete their course or stop at the discretion of the supervising physician.

This decision applies only to the conduct of the Solidarity trial and does not apply to the use or evaluation of hydroxychloroquine in pre or post-exposure prophylaxis in patients exposed to COVID-19

The use of hydroxychloroquine and chloroquine are accepted as generally safe for use in patients with autoimmune diseases or malaria.

US FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine

On June 15, the U.S. Food and Drug Administration (FDA) revoked the emergency use authorization (EUA) that allowed for chloroquine phosphate and hydroxychloroquine sulfate to be used to treat certain hospitalized patients with COVID-19 when a clinical trial was unavailable, or participation in a clinical trial was not feasible. The FDA determined that chloroquine and hydroxychloroquine are unlikely to be effective in treating COVID-19 for the authorized uses in the EUA.

Additionally, in light of ongoing serious cardiac adverse events and other potential serious side effects, the known and potential benefits of chloroquine and hydroxychloroquine no longer outweighed the known and

potential risks for the authorized use.

Clinical trials continue to evaluate the potential benefit of these drugs in treating or preventing COVID-19.

FDA news release: FDA revokes emergency use authorization for Chloroquine and Hydroxychloroquine (15 June 2020)

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

There are now a total of 2 824 reports from all six WHO regions in the WHO Global of Individual Case Safety Reports database, VigiBase. The majority of reports are from the European region (64.1%) where 51.9% of the reports were classified as "serious", males accounted for 55.7% of the reports and females 38.8%. Most of the reports describe at least one drug or substance in the WHO Solidarity trial, i.e. hydroxychloroquine or chloroquine, azithromycin, remdesivir and lopinavir; ritonavir, as either suspected or interacting.

Some reports have also been received on other drugs known to be used in the treatment of COVID-19 disease. Tocilizumab and oseltamivir were the most reported (>100 reports) among these drugs. Patient ages were similar between drugs, although oseltamivir had the lowest median age.

A descriptive analysis of the other new reports is available at this link:

A descriptive analysis of the new reports (17 June)

Vaccines

Human challenge studies

In view of the urgent need to develop vaccines against the SARS-CoV-2 virus, the WHO convened an Advisory Group (AG) to consider the feasibility, potential value and limitations of establishing a closely monitored challenge model of experimental SARS-CoV-2 infection and illness in healthy young adult volunteers.

The report of the AG details issues that make such a model special and daunting to establish, such as its potential to cause severe and fatal illness and its high transmissibility. The report provides solutions to address many of the issues. Detailed instructions for selection of potential challenge viruses, guidelines for manufacture, formulation, and presentation of challenge doses, ways to achieve containment of the virus and to prevent transmission to household and community contacts have been proffered.

Prudent strategies for stepwise model development and for detailed measurement of immune responses and virus shedding are offered. Such a model could potentially demonstrate protection against virus shedding

and/or clinical illness induced either by prior infection with the challenge virus or by immunization with a candidate vaccine. A limitation of the model is that evidence of efficacy obtained in healthy young adults cannot *per se* be extrapolated to predict vaccine efficacy in certain high-risk target populations such as the elderly or adults with underlying diabetes, cardiac and pulmonary conditions; so, this issue was not addressed in depth by the AG.

Attitudes for undertaking Stage 1 studies to establish the model are influenced by whether or not a proven effective treatment exists that can prevent moderate disease from progressing to serious illness and death, with one half of the AG cautioning to await such a treatment as a prerequisite for starting and others urging an initiation of challenge studies even absent such a treatment.

Ongoing controlled clinical trials of potential therapeutic interventions will be closely watched for signs of a breakthrough to obtain an effective treatment, while steps to manufacture GMP challenge inocula proceed.

Report is available **for public comments by 23 June, 18h00 CET**:

> Report from the WHO Advisory Group on Human Challenge Studies: Feasibility, potential value and limitations of establishing a closely monitored challenge model of experimental COVID-19 infection and illness in healthy young adult volunteers

New international guidance on quality, safety and efficacy of DNA vaccines

Based on the progression of several DNA vaccines to clinical evaluation and increasing awareness of the potential utility of DNA vaccines in outbreak responses, WHO had initiated a process for revision of its existing guidelines on quality, safety and efficacy of DNA vaccines prior to the COVID-19 pandemic. As vaccine development against SARS-CoV-2 includes DNA vaccine candidates, revision of the Guidelines is especially timely. The report of a meeting on the proposed revisions, and an accompanying commentary, have just been published and are available.

> DNA vaccine meeting report: WHO informal consultation on the guidelines for evaluation of the quality, safety, and efficacy of DNA vaccines, Geneva, Switzerland, December 2019 (18 June 2020)
>
> Comment: New international guidance on quality, safety and efficacy of DNA vaccines (18 June 2020)

The revised guidelines focus on biologically manufactured bacterial plasmid DNA for use in humans, and address aspects related to control of manufacture and characterization, approaches to nonclinical and clinical testing, and information that may be required by national regulatory authorities for approval of clinical trials or licensure.

A final draft of the guidelines was made available for comments by 13 June 2020. An extraordinary meeting of the Expert Committee on Biological Standardization will, after review of further comments received, consider approval of the revised guidelines.

The revised Guidelines are considered unlikely to be applicable to RNA vaccines, and development by WHO of separate document(s) is underway.

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 (18 June)

Convalescent plasma

On June 12, AFRO held a virtual meeting on "the impact of the COVID-19 pandemic on maintaining blood supply in the WHO African Region" where the Blood and other Products of Human Origin (BTT) Team, WHO

Headquarters, gave presentation on the WHO Interim Guidance on Maintaining blood supply during COVID-19 pandemic and collection of COVID-19 Convalescent Plasma (CCP). The meeting was attended by all WHO country offices and National Blood Transfusion Services from African Region.

On June 15, 2020, an "Action Framework for Blood Products 2020-2023" and the WHO interim guidance were presented in a Webinar on "Obtaining a safer blood and sustainable blood supply during COVID-19 pandemic, held by the Department of Health National Voluntary Blood Services Program, Philippines attended by more than 500 participants.

The Iranian Blood Transfusion Organization through their E-Newsletter, Vol 22, May 2020, reported the preliminary results of CCP clinical trial on 200 COVID-19 patients conducted in Iran, that shows the efficacy of CCP therapy in treatment of critically-ill COVID-19 patients in terms of better lung CT score and other clinical improvement. The authors concluded that administration of CP is safe, reduces mortality, length of hospital stay and rate of intubation.

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

WHO Working Group on Assays and Reference Preparations

The Translational Health Science and Technology Institute, India, reported on the establishment of a national COVID-19 biorepository supported by the Indian government in the 10 June meeting. The aim is to create a bio resource for COVID-19 with collaboration of multiple institutes / laboratories in India, including collection and characterization of SARS-CoV-2 specimens / samples from various sites of patients; studying the type and duration of immune responses; growing, maintaining and distributing viral strains and inactivated viruses; developing national standards panel for SARS-CoV-2 serology; and developing control panels for IVDs.

Currently several panels are established including sera, plasma and PBMC isolated from blood. A serum panel for COVID-19 serodiagnostics includes 100 samples from patients who tested positive for SARS-CoV-2 by RT-PCR stratified by different timings post-symptoms.

The repository is established as a national resource and requests for the panels are reviewed by a national Committee. The possibility to provide the sera panels to laboratories outside India will be referred to the government for decision.

Vaccine developers were invited to join the 17 June meeting. A review of topics covered since the last call with developers was presented.

The review covered progress with commercially availability of full-length spike protein; improved expression and stability of prefusion-stabilised spike protein; the development of a SARS-CoV-2 virus with a reporter gene for use in high throughput neutralization assays; national serology standards in China and India; the development of multiplex serological assays that distinguish between coronaviruses that infect humans; the development of antibody effector and isotype assays; and T-cell assays for SARS-CoV-2. A progress report was also presented on development of a WHO International Standard for SARS-CoV-2 antibodies.

A candidate reference reagent has been developed by NIBSC, UK, and an international collaborative study to evaluate the suitability of the material will start in July with participation from over 50 laboratories.

WHO Working Group on Animal Models

Summary of progress: WHO COVID-19 modelling ad-hoc Expert WG (26 March – 01 June 2020)

More than 120 participants globally are actively contributing to the Expert Group. The goal of the group is to advance the development of COVID-19 medical countermeasures (vaccines, therapeutics and/or drugs). This is being achieved by providing a platform to share data to help reduce duplication of effort and to accelerate learning by sharing outcomes in a secure and confidential workspace. In addition, the principles of reduction, refinement and replacement are being addressed by this international effort.

The outcomes to date are:

1) Despite digital modelling predictions based on ACE2 genetic analysis, some animal species predicted to be susceptible are seemingly resistant, whilst others are susceptible when not expected to be. Pathogenesis studies have, however, been conducted mainly in human ACE2 transgenic mice, hamsters, ferrets and various NHP models, including Rhesus macaques, cynomolgus macaques and African green monkeys. Across many laboratories in the world, using different SARS-CoV-2 isolates, the results in these species have been remarkably reproducible and indicate mild to moderate disease with pulmonary pathology, virus shedding in upper and lower respiratory tract and, in some studies, rectal swabs, some variable weight loss and in all cases, full recovery.
2) Different methods are being utilized to achieve expression of human ACE2 in laboratory mice including transgenesis under the control of different promoters and vectored delivery prior to infection. These methods have resulted in a pathogenesis range from either mild or severe disease, depending on the promotor utilized. These findings indicate that the levels and pattern of expression of human ACE2 in mice are a key modulator of SARS-CoV-2 pathogenicity in this model.

   Other studies in mice have suggested that induced immune suppression can render a fully resistant wild strain of mouse susceptible to infection with SARS-CoV-2. This suggests that although ACE2 receptor affinity is an important factor in susceptibility, immune suppression is also pivotal in host susceptibility
3) Several therapeutics have been tested in animal models. Some monoclonal antibodies and antibody fragments have demonstrated protection in mouse and hamster models. A study evaluating remdesivir in non-human primates was also presented. Chloroquine and hydroxychloroquine failed to show any therapeutic effect in NHP and hydroxychloroquine has not been found to be effective in a complex human model system of respiratory epithelium.
4) Several vaccines have been shown to be immunogenic and protective, by reducing lower respiratory tract virus burden in NHPs. Some members of the working group have suggested that an added value of vaccine candidates would be the ability to generate mucosal immunity, including IgA, to improve protection of the upper respiratory tract.

Summary of progress made by the WHO COVID-19 modelling March – 04 June 2020 (04 June 2020)

Global animal laboratories capacities to support vaccine and therapeutic evaluation

WHO surveyed networks of laboratories to map out global animal laboratory capacity around the world to potentially help with accelerating vaccine and therapeutic evaluation.

The outcome of the survey: Global animal laboratories capacities to support vaccine and therapeutic evaluation (16 June 2020)

Pathogenesis studies

In the 11th June meeting it was reported that cats are susceptible to infection with SARS-CoV-2. After intranasal and *per os* infection, virus can be recovered from nasal and rectal swabs. Lung pathology occurs

but no clinical symptoms. Transmission to cage mates was demonstrated.

Another study showed African green monkeys were susceptible to infection using an aerosol challenge. Virus titre was higher in the gastrointestinal tract than respiratory tract, and no or only mild clinical symptoms occurred. However, PET/CT scanning was found to be an effective way to monitor lung pathology and was suggested as a useful tool to use in future immunization/challenge studies.

In a third report a mouse-adapted SARS-CoV-2 virus was described. Changes predicted to enable the virus to infect mouse cells had been engineered into the spike protein. This was tested first in mouse cell-cultures and, on the basis of positive results, tested in balb/c mice. Data were presented to show that the mouse-adapted virus, unlike parental virus, caused weight loss with respiratory symptoms in older mice. Epithelial cell tropism was demonstrated in the lung. The engineered virus is now being serially passaged in balb/c mice. The passage level 10 virus is causing significantly more weight loss and lung pathology. The development of a mouse-adapted challenge virus is likely to be of benefit for testing therapeutics and vaccines.

The final report was of an outbreak of SARS-CoV-2 in mink farms in the Netherlands. Based on sequence analysis the virus had likely been introduced from infected farm workers. Feral cats living in the vicinity of the farms were also found to be infected with SARS-CoV-2. Based on these findings the potential need for veterinary vaccines was raised in discussion.

Meeting with vaccine developers

The 18 June meeting was open to vaccine developers and at least 205 participants joined the meeting. Experts from the WHO Animal Models summarized current scientific understanding of animal models that have been characterized after experimental infection with SARS-CoV-2 virus. It was noted that experts within the Group had shared data in an unprecedented way to accelerate scientific understanding and to reduce duplication of effort. Current understanding of mouse models, hamsters, ferrets, non-human primates, cats, pigs, dogs and chickens was reviewed.

The priorities for the next 6 months for the Working Group were also presented. These include whether vaccines can prevent virus shedding after challenge; to test whether higher virulence of the SARS-CoV-2 virus is emerging; models to test for vaccine mediated enhanced disease; to develop methods to induce more severe disease in animal models; to encourage international standardization by sharing of protocols and reagents; and to identify laboratories that can conduct these studies.

Vaccine developers were especially interested to learn whether significant mutations would be introduced during passage of the SARS-CoV-2 virus to generate sufficient stocks for animal studies. The experts acknowledged this is a risk, and has been seen in some laboratories working with animal models. The advice from experts was that deep sequencing would be advisable of the virus stock and compared with the starting material.

Another question from several developers was whether a model was available to study the possibility of vaccine mediated enhanced disease. The experts responded that whilst studies are in progress, data are not yet available to answer this question. Several groups expect to have results within 4-8 weeks on potential models.

Supply chain updates from WHO HQ and Regional Offices

Emergency Global supply chain system (COVID-19) catalogue

The following catalogue lists all medical devices, including personal protective equipment, medical equipment, medical consumables, single use devices, laboratory and test-related devices that may be requested through the COVID-19 Supply Portal.

Emergency Global supply chain system (COVID-19) catalogue (18 June 2020)

Shipments from UN partners

Shipments to countries continue from the UN supply chain consortium, including over 100 shipments to countries in WHO regions. Requests from countries have increased, most notably, from countries and entities that have not typically been eligible for support from UN procurement initiatives. Discussions are underway regarding options on scaling out existing mechanisms to expand their reach, particularly to distribute PPEs, diagnostics and equipment, such as oxygen equipment and ventilators. Demand continues to be constrained for these products.

Shortages

Processes to report shortages that are included in publicly available databases often cannot capture information early enough in an environment where demand spikes are sudden and where other changes that disrupt supply chains, such as export restrictions, are frequent and unpredictable. WHO recognizes the need to proactively seek information about shortages related to COVID-19 through its networks.

Currently, manufacturing levels are informally reported to have returned to 80% or more of their prior production levels and transportation is slowly resuming. However, as pockets of new infection have emerged in manufacturing countries, monitoring efforts will increase on identifying risks to critical products, including finished products and active pharmaceutical ingredients.

For candidate products with promising preliminary results from clinical trials, including convalescent plasma, procurers are encouraged to perform realistic quantification scenarios about the potential use of these products. Speculative purchasing and hoarding can skew information on true demand and need, which delays necessary responses, such as confirming estimates to scale up production or respond with approaches for fair allocation.

Quality assurance in supply chain

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

Watch list

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

- Antibiotics: azithromycin, levofloxacin, metronidazole, amoxiclav, piperacillin, tazobactam
- epinephrine and norepinephrine
- Benzodiazepine sedatives: midazolam and lorazepam
- Nonbenzodiazepine sedatives: propofol

- Antipsychotics: haloperidol
- Neuromuscular relaxants: succinylcholine, atracurium, or vecuronium.
- Opioids: morphine and fentanyl
- Malaria treatments: hydroxychloroquine, chloroquine, artemether-lumafantrine, artemisinin-based combination therapies, sulfadoxine-pyrimethamine + amodiaquine)
- HIV: Lopinavir/ritonavir
- NCD: Metformin and insulin
- Antipyretics: paracetamol (aka acetaminophen)
- Corticosteroids: salbutamol (aka albuterol) inhalers, dexamethasone
- PPE
- Oxygen and related equipment
- Ventilators

Medical Devices

Important new publications that include medical devices are listed below:

1. WHO technical specifications for pressure-swing-adsorption (PSA) Oxygen Plants (06 June 2020)
2. Most recent guideline on Clinical management of patients (27 May 2020)
3. Guideline on the use of masks both for community and health care workers (05 June 2020)
4. Guideline on the use of imaging diagnostics, ultrasound, X ray and CT complementary to IVDs (05 June 2020)
5. The call for innovative technologies for low resource settings in the context of COVID
6. The biomedical inventory survey for oxygen related devices:

   Username: biomedequipment, Password: facilityoxygen20

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

The PPE experts meeting is developing QA and updating the technical specifications and related standards for PPE, new documents will be available in the next few days.

Medical device page: Priority medical devices for COVID prevention, diagnostic and management

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