# 15th WHO Regulatory Update on COVID-19

**31 July 2020**

World Health Organization

## Key Messages

This week marks 6 months since WHO declared COVID-19 a public health emergency of international concern. The speed of product development has been extraordinary. Currently, over 165 candidate vaccines are at some stage of development. Of these, about 25 vaccine candidates are in human trials. We have also learnt a lot about therapeutics, in particular that there are different phases of this disease and the treatment needs to be tailored to each phase.

Aggressive diagnostic testing to identify patients infected with SARS-CoV-2 is critical to control the pandemic. More than 700 tests have been developed, including molecular, serological and antigen detection tests. So far, over 10 billion tests have been performed.

Along with accelerating research and ensuring manufacturing capacity, WHO is also working with countries to develop regulatory capacity, as well as supportive policies and delivery channels. These will be essential to get successful products out to people.

## Highlights and main issues

- A special insert related to COVID-19 in the "2nd Edition of the Trilateral Study WHO-WIPO-WTO on Promoting Access to Medical Technologies and Innovation: Intersections between Public Health, Intellectual Property and Trade", which was launched on 29 July, shares practical experience and understanding of a wide range of policy instruments to help address the multi-dimensional challenges of the response to the COVID-19 pandemic.
- International regulators have published a report on the acceptability of various primary endpoints in the clinical trials conducted for the development of treatments for COVID-19.
- An AVAREF Webinar on 29 July presented AVAREF and its emergency joint-review process to more than 100 product developers.
- Two Question and Answer documents on the WHO EUL procedure have been posted.
- WHO has published draft Target Product Profiles for treatment of COVID-19 in hospitalized patients for comment.
- Encouraging results from two phase I/II COVID-19 vaccine trials have been published.

# 15th WHO Regulatory Update on COVID-19

## Contents


Key Messages ..... 1
Highlights and main issues ..... 1
Promoting Access to Medical Technologies and Innovation ..... 2
COVID-19 Technology Access Pool (C-TAP) ..... 3
Alignment of approaches by regulatory groups ..... 3
Agreement on acceptable endpoints for clinical trials of therapeutics ..... 3
AVAREF webinar ..... 4
*In vitro* diagnostics ..... 4
WHO EUL submissions and listing update ..... 5
IVDs listed by National Regulatory Authorities in IMDRF jurisdictions ..... 5
Therapeutics ..... 6
Achievements in the first 6 months since the declaration of PHEIC ..... 6
WHO Expression of Interest for manufacturers of dexamethasone and remdesivir ..... 6
WHO target product profiles for COVID-19 therapeutics ..... 6
Solidarity trail: Sofosbuvir/Daclatasvir not to be included ..... 7
Research mapping of candidate therapeutics ..... 7
Adverse drug reactions ..... 7
Vaccines ..... 8
Achievements in the first 6 months since the declaration of PHEIC ..... 8
Encouraging results from phase I/II COVID-19 vaccine trials ..... 8
Landscape of candidate vaccines for SARS-CoV-2 ..... 9
Convalescent plasma ..... 9
Research protocols, assays and reference standards ..... 10
WHO Working Group on Assays and Reference Preparations ..... 10
WHO Working Group on Animal Models ..... 11
Supply chain updates ..... 12
Shipments from UN partners ..... 12
Shortages ..... 12
Watch list and active shortages ..... 12


## Promoting Access to Medical Technologies and Innovation

International cooperation on public health is inherently multi-dimensional, with a focus on building effective health systems. It is dynamic and responsive to the demands of countries around the globe. The pandemic has from its outset raised issues at the crossroads of public health policy, trade policy and the framework for and the management of innovation, including those relating to intellectual property (IP) rights.

The World Health Organization (WHO), the World Intellectual Property Organization (WIPO) and the World Trade Organization (WTO) have been working closely together to support international cooperation on health, IP and trade issues in a transparent and holistic manner. For example, generic manufacturers in Bangladesh have begun producing a generic version of remdesivir to treat COVID-19, which is patented in a number of other countries, benefitting from the transition period under the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement). TRIPS Agreement currently exempts least-developed countries from implementing patent protection for

pharmaceutical products and from protecting clinical trial data.

2nd Edition of the Trilateral Study WHO-WIPO-WTO on "Promoting Access to Medical Technologies and Innovation: Intersections between Public Health, Intellectual Property and Trade", launched on 29 July, includes a special insert related to COVID-19, sharing practical experience and understanding of a wide range of policy instruments to help address the multi-dimensional challenges of the response to the COVID-19 pandemic.

> WHO News Release: WHO, WIPO, WTO launch updated study on access to medical technologies and innovation (29 July 2020)
>
> 2nd Edition: WTO-WIPO-WHO publication on Promoting Access to Medical Technologies and Innovation – Intersections between public health, intellectual property and trade

## COVID-19 Technology Access Pool (C-TAP)

The COVID-19 Technology Access Pool, or C-TAP, compiles voluntarily shared COVID-19 health technology knowledge, intellectual property and data. On 29 May, WHO and Costa Rica launched the C-TAP call to action - to encourage voluntary sharing of knowledge, intellectual property and data necessary to respond to COVID-19. The aim was to build on momentum from the World Health Assembly and get early buy-in to the concept.

Forty countries immediately expressed interest. More countries are now expressing interest - including an encouraging number of pharmaceutical producing countries. Since then, WHO has been working with key stakeholders, including industry and intellectual property experts, to design an operational plan. WHO aims to launch the plan in late summer, with a presentation to countries and consultations with potential partners.

The implementing partners of C-TAP are: Medicines Patent Pool, Open COVID pledge, Tech Access Partnership and Unitaid. C-TAP is not a quick fix but a mid- to long-term approach to improving technology transfer approaches. It is complementary to other COVID-19 initiatives, such as the ACT-Accelerator. It builds on existing initiatives like the Medicines Patent Pool.

> COVID-19 Technology Access Pool (C-TAP)

## Alignment of approaches by regulatory groups

### Agreement on acceptable endpoints for clinical trials of therapeutics

International regulators have published a report on the acceptability of various primary endpoints in the clinical trials conducted for the development of treatments for COVID-19.

The report summarizes the main outcomes of the second workshop on COVID-19 therapeutics and clinical trials organized under the umbrella of the International Coalition of Medicines Regulatory Authorities (ICMRA). The workshop was co-chaired by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) and European Medicines Agency (EMA) on 20 July 2020.

Many developers of medicines for the treatment of COVID-19 have already or are in the process of conducting clinical trials and have approached their regulatory authorities with proposals for phase III clinical trials. An agreement by regulators on acceptable endpoints will facilitate rapid and consistent implementation of future clinical trials for COVID-19 medicines across the world.

For hospitalized patients with moderate to severe COVID-19, a range of suitable primary endpoints is available to measure the clinical benefit of investigational therapeutics for COVID-19 and support

regulatory decision-making. While the workshop participants agreed that mortality is not the sole acceptable primary endpoint for these patients, mortality data should still be collected as a key secondary endpoint in all trials that do not plan to primarily use this outcome.

For outpatients with mild COVID-19, regulators agreed that mortality as the primary endpoint may not be suitable. Instead, the rate of progression to severe disease and the proportion of patients not hospitalized at a pre-specified time point may be more appropriate, depending on the primary objective of the study.

### AVAREF webinar

The African Regional Office hosted an AVAREF Webinar on 29 July 2020 to present AVAREF and its emergency joint-review process. The target audience was product developers and more than 100 attended.

AVAREF has been successful as a platform to obtain, from across the continent of Africa, streamlined reviews of clinical trial applications with predictable timelines not only from national regulatory authorities but also national ethics committees. The advantages of using AVAREF were illustrated by testimony from a product developer. An emergency procedure for joint reviews of COVID-related clinical trial applications developed by AVAREF was presented in detail. A lively question and answer session followed.

AVAREF Guideline for joint and assisted reviews of clinical trial applications

AVAREF Strategy and Guidance for Emergency Preparedness (May 2020)

## WHO Emergency Use Listing (EUL)

Two Question and Answer documents on the WHO EUL procedure have been posted. One set of Q&As addresses issues that apply to all three product streams (IVDs, medicines, vaccines), and the second set are Q&As specific for vaccines.

WHO Emergency Use Listing of Vaccines

Q&A for Guidelines on Emergency Use Listing Procedure

Q&A for Use of Emergency Use Listing procedure for vaccines against Covid-19

## *In vitro* diagnostics

The WHO Prequalification Unit is assessing products for Emergency Use Listing (EUL) for candidate in vitro diagnostics (IVDs) to detect SARS-CoV-2.

On 3 July 2020 the EUL scope will be expanded to antibody detection enzyme immunoassays. The following IVDs are therefore 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.

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

## WHO EUL submissions and listing update

Applicants are asked to submit their applications for assessment based on WHO instructions and requirements for NAT and Ag detection RDTs and IVDs detecting antibodies to SARS-CoV-2.

50 expressions of interest for NAT assays, 16 for antibody detection RDTs have been received so far.

The status of each application: update (27 July 2020)

15 products have been listed as eligible for WHO procurement based on their compliance with WHO EUL requirements: (no newly listed IVD since 17 July 2020)

| Date Listed | Product name | Product code(s) | Manufacturer |
|---|---|---|---|
| 9 July 2020 | COVID-19 Coronavirus Real Time PCR Kit | JC10223-1NW-50T | Jiangsu Bioperfectus Technologies Co.,Ltd |
| 6 July 2020 | Simplexa COVID-19 Direct and Simplexa COVID-19 Positive control Pack | MOL4150, MOL4160 | DiaSorin |
| 23 June 2020 | Xpert® Xpress SARS-CoV-2 | XPRSARS-COV2-10 | Cepheid AB |
| 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. |

## IVDs 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.

The most recent update (28 July 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.**

# Therapeutics

## Achievements in the first 6 months since the declaration of PHEIC

Collectively, we have learnt a lot about how to care for people. There are different phases of this disease and the treatment needs to be tailored to each phase. The vast majority of people have mild or moderate symptoms, and a large number of people don't even have symptoms. A small proportion develop severe disease. They need to be hospitalized and may need oxygen and respiratory support like ventilators. We are learning that some patients who have recovered have longer terms problems.

Anti-viral drugs: a large variety of pre-existing drugs that were thought could be effective have been tested. Most have been shown to be ineffective, except for Remdesivir which shows a modest reduction in hospital stay, but no reduction in mortality of hospitalized patients. The trials on this – including Solidarity Trial – are on-going. WHO is carrying out a systematic review on Remdesivir.

Managing immune response: SARS-CoV-2 induces a strong immune response that we need to manage. Dexamethasone (orally or intravenously) has been shown to reduce mortality in people on oxygen/ventilation. WHO is carrying out a systematic review of steroids.

> Q&A: Dexamethasone and COVID-19 (25 June 2020)

Thrombosis: there are reports of high rates of blood clots in patients who are seriously ill with COVID-19, and anti-thrombosis drugs have been shown to be effective.

Monoclonal antibodies, which prevent virus from binding to cells, are going into clinical trials for prevention and treatment.

## WHO Expression of Interest for manufacturers of dexamethasone and remdesivir

As indicated in the 14th Regulatory Update, WHO issued an Expression of Interest (EOI) for manufacturers of dexamethasone and remdesivir products on 10 July.

The aim of the EOI invitation is to increase the range of selected products and sources available. Dossiers for these products may be submitted by manufacturers for assessment by the WHO Prequalification Team. Specifications for characteristics and formulations of the two invited products are outlined in detail in the EOI.

Once the Prequalification Team is satisfied that WHO recommended standards for quality and safety / efficacy are met, the product (as produced at the specified manufacturing site) is added to the WHO List of Prequalified Medicinal Products. This will allow procurement agencies and others to confidently obtain and recommend use of specific dexamethasone and remdesivir products in patient care.

> Invitation to Manufacturers to submit EOI for product evaluation of **dexamethasone and remdesivir**

## WHO target product profiles for COVID-19 therapeutics

WHO has published Draft Target Product Profiles (TPP) for treatment of COVID-19 in hospitalized patients. These TPPs describes the preferred and minimally acceptable profiles for therapeutic agents for the treatment of those hospitalized with COVID-19, ranging from mild through moderate to severe to critically ill patients in three sets of TPPs.

WHO is welcoming comments on the draft TPP

> Draft TPP for treatment in hospitalized patients
>
> Please use the comment form and send comments to salamik@who.int by 14 August 2020

### Solidarity trail: Sofosbuvir/Daclatasvir not to be included

Sofosbuvir (SOF) and daclatasvir (DCV) are antiviral drugs, which are approved for treatment of Hepatitis C infection. There are publications of *in-silico* studies, i.e., performed on computer or via computer simulation, suggesting docking affinity for sofosbuvir and daclatasvir to structural proteins of SARS-CoV-2. In vitro evaluation of both drugs is in progress. Preliminary results of 3 clinical studies in Iran are also available.

A WHO consultation discussed the potential for SOF/DCV to be tested in a larger clinical study. Although this combination therapy has shown some encouraging results in small trials, it was noted there is not enough data to know which drug and what dose regimen would be effective since SOF/DCV was given in combination with Kaletra in the Iranian trials.

Further, according to the in vitro data presented, SOF will not achieve an effective concentration is plasma. It was suggested, going forward, to explore if there is any synergistic effect when combined with other antivirals. Animal studies will be very important to provide a proof of concept in this sense. The consultation also noted there is a need for more studies to define the adequate dose regimen of DCV before considering moving to phase III. More *in vitro* and *in vivo* data are required to support dose selection.

It was concluded there is not enough preclinical and clinical evidence to consider SOF/DCV to be included in large clinical trials like Solidarity.

Informal consultation on the potential inclusion of SOF/DCV in a clinical trial (19 June 2020)

### Research mapping of candidate therapeutics

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 pharmacovigilance summary (in the 13th Regulatory Update), 473 new case reports have been submitted to VigiBase, the WHO Global Database of Individual case Safety Reports.

Most of the reports describe at least one drug or substance originally included in the WHO Solidarity trial, i.e. hydroxychloroquine (in some regions replaced by chloroquine), azithromycin, remdesivir and lopinavir;ritonavir as either suspected or interacting. There are also reports with other drugs used in the treatment of COVID-19 disease.

Cumulatively, there are a total of 4 324 reports from all six WHO regions with the large majority from the European region (51.5 %). 52.8 % of the reports were classified as “serious”. In line with males being more affected by COVID-19 infection globally, all drugs, except chloroquine and oseltamivir, are reported more for men than women.

A descriptive analysis of the new reports (22 July 2020)

# Vaccines

## Achievements in the first 6 months since the declaration of PHEIC

Currently, **over 165 candidate vaccines** are at some stage of development. Of these, about **25 vaccine candidates are in human trials**. AstraZeneca, Moderna and CanSino are in or starting Phase III; a Russian candidate vaccine is entering this phase too. There are several others currently in phase I/II, which will enter phase III in the coming 2 months.

There is a very robust pipeline – the more candidates, the more opportunities for success (typically success rate of candidate vaccines is 10%). The candidate vaccines are of various types – virus vaccines using live attenuated virus, viral vector vaccines, protein vaccines, and **RNA and DNA vaccines, which are completely new platforms.**

**COVAX**, the vaccines pillar of the Access to COVID-19 Tools Accelerator (**ACT-Accelerator)**, convened by CEPI, Gavi and WHO, is speeding up the search for an effective vaccine for all countries. At the same time, it is supporting the building of manufacturing capabilities, and buying supply ahead of time so that 2 billion doses can be equitably distributed by the end of 2021.

Seventy-five countries submitted expressions of interest in the **COVAX Facility**, joining another 90 countries that could be supported by the COVAX Advance Market Commitment (AMC). The COVAX Facility is a mechanism designed to guarantee rapid, fair and equitable access to COVID-19 vaccines worldwide. The COVAX Facility is a key part of the vaccine pillar of ACT-Accelerator.

WHO is also developing a **global allocation framework,** for vaccines and other COVID-19 tools**,** based on fair and equitable access principles. The framework is currently being developed with Member State input.

Global allocation framework: presentation for Member States Briefing (23 July 2020)

WHO press release on COVAX facility (15 July 2020)

## Encouraging results from phase I/II COVID-19 vaccine trials

The results of two early phase COVID-19 vaccine trials have been reported, one from investigators at the Jenner Institute at Oxford University (Oxford, UK), with support from AstraZeneca, and the second from investigators supported by CanSino Biologics in Wuhan, China.

Both groups used an adenoviral vector, and both report the vaccine achieving humoral responses to the SARS-CoV-2 spike glycoprotein receptor binding domain by day 28 as well as T-cell responses. Both report local and systemic mild adverse events such as fever, fatigue, and injection site pain. In neither trial was a severe adverse event reported.

An accompanying commentary on the publications notes that the results of both studies augur well for phase III trials. Overall, the results of both trials are broadly similar and promising, notwithstanding differences in the vector, in the geographical locations of the populations studied, and the neutralization assays used.

Both trials used adenovirus vectors to deliver and study the COVID-19 vaccine. The platform only achieved European Commission regulatory licensure on July 1, 2020, with the Ebola vaccine. Much remains unknown about these and other COVID-19 vaccines in development, including longevity of response and immunogenicity in older adults or other specific groups, such as those with comorbidities who are often excluded from clinical trials, or ethnic or racial groups more severely affected by COVID-19.

The Lancet commentary on results from phase I/II COVID-19 vaccine trials (20 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 (31 July 2020)

## Convalescent plasma

Since early 2020, Member States in multiple WHO regions have requested advice from WHO on managing blood systems during the SARS-CoV-2 pandemic and potential therapeutic use of COVID-19 convalescent plasma. In response, the Blood and other Products of Human Origin (BTT) team within the Technical Standards and Specifications Unit of the Health Products Policy and Standards Department developed Interim Guidance in this area that WHO published initially on 20 March 2020 and updated on 10 July 2020. To enhance awareness of the recent guidance, the BTT hosted an open international Webinar on 28 July 2020 where two experts discussed the relevant policy and scientific issues.

Speaking as a consultant to the BTT, Jay Epstein, M.D., Senior Advisor for International Blood Regulatory Affairs at the US FDA, summarized the 10 July 2020 WHO "Guidance on maintaining a safe and adequate blood supply during the coronavirus disease 2019 (COVID-19) pandemic and on the collection of COVID-19 convalescent plasma." He explained the identified strategies to reduce the potential risk of transfusion transmission of SARS-CoV-2, to protect blood donors and staff of blood centers against exposure to the virus, to mitigate the impact of reduced blood donations and of disruptions to blood center operations, and to balance demand and supply of blood for transfusion. He emphasized a) that preparation of COVID-19 convalescent plasma should comply with recognized standards for quality and safety; and b) that this product currently is experimental and therefore should be used only in randomized controlled trials or structured observational studies.

Arturo Casadevall, M.D., Ph.D., a professor at the Johns Hopkins School of Public Health, USA, next presented a talk on the "Scientific rationale and clinical experience with experimental treatment with COVID-19 convalescent plasma." He reviewed the history of successful use of convalescent plasma to prevent and treat a number of infectious diseases and the known mechanisms of action of antibodies. He summarized the clinical experience with COVID-19 convalescent plasma noting the encouraging findings from the limited available publications of case studies with matched controls and randomized clinical trials. He commented on the current role of COVID-19 convalescent plasma in current therapy and its future role in informing the development of immune globulins, monoclonal antibodies and vaccines against SARS-CoV-2.

In a lively question and answer period that followed the presentations, the received questions focused mainly on practical issues with collection of COVID-19 convalescent plasma in resource constrained settings.

Live webinar on "Strengthening Blood Systems through Effective Blood Regulation" will be held from 3rd to 6th August 2020. The objective of the webinar is to sensitize blood regulators and operators and other national stakeholders on the importance of blood regulation, and to introduce the best practice and key elements of an effective blood regulatory system as the first step to build blood regulatory capacities in Member States.

Information on the live webinar: 3 - 6 August 2020

# Research protocols, assays and reference standards

## WHO Working Group on Assays and Reference Preparations

Data analyzing antibody responses to SARS-CoV-2 infection and a study of SARS-CoV-2 mutations

22 July 2020

A study from Kings College, London, UK assessed the kinetics, magnitude and longevity of the antibody response and how neutralizing antibody (nAbs) relates to disease severity, using ELISA (target S, RBD and N protein) and neutralization assays, in a cohort study of Health Care Workers.

Key findings were that all individuals with a measurable antibody response had some level of nAbs (high to low); that the severity of disease affected the peak of nAbs but not kinetics, the higher peak ID50 the longer good titers last (2-3 months); and that IgM and IgA decrease in 3-4 weeks, while IgG and nAb wane more slowly.

A study from Icahn School of Medicine at Mount Sinai, New York, USA found that SARS-CoV-2 infection induces Ab responses that are stable for at least 3 months. More than 51 000 blood donors were screened by ELISA. In PCR confirmed donors, 99.5% were antibody positive, whereas in COVID-19 suspected donors (without PCR confirmation) 38.2% were antibody positive.

The impact of mutations in SARS-CoV-2 on viral infectivity and antigenicity was presented by NIFDC, China. The spike protein of SARS-CoV-2 has been undergoing mutations and is highly glycosylated. It is critically important to investigate the biological significance of these mutations, especially meaningful for vaccine development. The group investigated 80 variants and 26 glycosylation site modifications for infectivity and reactivity to a panel of well characterized monoclonal Abs and convalescent sera.

Key findings were that most variants with amino acid change in the RBD were less infectious, but some variants outside the RBD were found to be more infectious; also that glycosylation plays important role for viral infectivity. These findings could be of value in the development of vaccine and therapeutic antibodies.

Studies analyzing the immune response to SARS-CoV-2

29 July 2020

Leveraging blood donor networks to study SARS-CoV-2 immunity provided access to large populations of healthy donors to investigate 1) whether any donations were viremic and infectious, 2) whether they can inform sero-epidemiology studies, 3) whether convalescent plasma is efficacious, 4) how common is an ineffective immune response post natural infection, and 5) neutralizing antibody persistence post infection.

All samples from blood donors were tested by an US FDA approved ELISA and a subset were tested by reporter gene virus neutralizing antibody test. Blood donors represent a large population for sampling and studies; a significant minority of recovered COVID-19 cases lack detectable binding and neutralizing antibodies; strategies can be deployed to maximize the yield of COVID-19 convalescent plasma.

It was suggested that the results of this study showed that it will be important to take serial samples in vaccine efficacy trials to investigate how long neutralizing antibody can be maintained.

A second presentation reviewed T cell assays for detection of SARS-CoV-2 specific T cells and selection of assays for analyzing immune responses in natural infection and phase III CTs and assay validation. It was suggested that induction of SARS-CoV-2 specific T cells could be a secondary or exploratory endpoint and/or correlate of protection in phase III CTs. T cell assay development and validation have been completed for detection of Th1 and Th2 responses. Peptide pools for SARS-CoV-2 spike protein have been developed; peptide pools for SARS-CoV-2 envelope, membrane and nucleocapsid proteins

are available for exploratory purposes.

Extensive experience is already being accrued evaluating vaccine-specific Th1/Th2 CD4 T-cell responses across many CTs. The use of a consistent reagent panel will be important to enable comparison of results across different vaccine platforms and from different parts of the world.

Adhering to protocols for sampling and sample delivery (via a cold chain) to maintain PBMC viability will also be critical.

## WHO Working Group on Animal Models

23 July 2020

The evaluation of Ad26 based vaccines against SARS-CoV-2 in rhesus monkeys was presented. Rhesus macaques (52), 10-12 weeks old, mixed males and females were included in the study. Single vaccination in week 0 with $10^{11}$ virus particles of Ad26 vectors with 7 spike (S) variants (N=32; N= 4-6 /group) and Sham controls (N=20). In week 6, SARS-CoV-2 challenge (IN+IT) with $10^5$ $TCID_{50}$ was given.

Main conclusions were: 1) Ad26-S.PP vaccination resulted in complete protection in the lung (6/6) and near complete protection in the upper respiratory tract (5/6); lack of anamnestic responses suggests minimal to no virus replication; 2) a second immunization with homologous Ad26 vectors typically increases Nab titers > 10-fold; 3) Nab titers were the strongest correlate of protective efficacy, consistent with a prior DNA vaccine study. Development plans for Ad26-S.PP (Ad26.COV2.S) includes a phase I-II study followed by phase III clinical efficacy study in September.

An assessment of the potential for vaccine-enhanced respiratory disease (VAERD) in mice was reported. The mRNA-1273 vaccine candidate was studied. Th1-biased CD4 and CD8 T cell responses were detected but no Th2 responses post-challenge with sub-protective vaccine doses. A positive control for VAERD using formalin/UV-inactivated SARS-CoV-1 was included. These data were assessed by regulators prior to initiation of phase III trials with the candidate vaccine, which started on 27 July 2020.

Finally, the SARS-CoV-2 susceptibility, transmission and reinfection in domestic cats was reported. Cats were infected with $10^6$ $TCID_{50}$ of SARS-CoV (IN and PO). There were no obvious clinical signs, no significant changes in blood cell parameters and no RNA in the blood (day 1 through 21 post infection (p.i.)) and urine (collected at necropsy). Transient shedding of viral RNA through oral/nasal/rectal cavities. Macroscopic and microscopic lesions in lung/trachea/bronchi with presence of viral RNA/antigen on days 4 and 7 p.i. but not on day 21 p.i. No interstitial pneumonia/ acute respiratory distress syndrome (ARDS) observed. Transmission to sentinels in 2 days.

In conclusion, the cat seemed to be a good model for “asymptomatic” SARS-CoV-2 infections. SARS-CoV-2 infection in cats induced humoral immune responses which provided protective efficacy (not sterile) against re-challenge.

29 July 2020

A study on imaging of SARS-CoV-2 infected NHPs was presented. Quantitative and semi-quantitative readouts such as percent change lung hyperdense volume, mapping radiographic evolution have been developed along with virology/immune responses. Further quantitation of the imaging readings is planned to optimize the model for studies of vaccines and therapeutics.

# Supply chain updates

## Shipments from UN partners

Shipments to countries continue from the UN supply chain consortium and the online portal is being used in an increasing number of countries.

## Shortages

Shortages for ICU products have increased in South and Latin America. PAHO is actively seeking alternate sources and regulatory flexibilities for countries that access medicines through the PAHO Strategic Fund. Suppliers have reported fragmented and chaotic demand signals from this region.

From the watchlist below, four have specific updates:

- Progress on resolving the malaria RDT shortage is ongoing, including tenders and activities to identify alternate sources. Manufacturing capacity from one of the main suppliers has also resumed the production for Malaria RDTs.
- Rifampicin has been added to the list. USFDA, WHO and the Global Drug Facility are investigating the problem.
- Lumefantrine is added to the list, noting an API problem with the producer in China.
- Remdesivir remains in shortage, with the main supplier not anticipating additional product until mid-August.
- Opioids are a particular problem in countries in Latin America and the Caribbean.

## Watch list and active shortages

WHO is still maintaining a watch list on the following products:

- RDTs for malaria diagnosis (production capacity reduced in some cases to produce diagnostic tests for COVID 19)
- 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, **Lumefantrine**
- TB: **Rifampicin tablets**
- NCD: Metformin and insulin
- Antipyretics: paracetamol (aka acetaminophen)
- PPE
- Oxygen and related equipment
- Ventilators
- **Experimental medicines: Remdesivir**
- Corticosteroids: salbutamol (aka albuterol) inhalers, dexamethasone