WHO Advisory Group Tasked to Consider the Feasibility, Potential Value and Limitations of Establishing a Closely-Monitored Challenge Model of Experimental COVID-19 in Healthy Young Adult Volunteers

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Objectives of the meeting

- Summarizing developments since the last Advisory Group meeting;
- Having research groups with plans for challenge models present the objectives for use of their models, once established (e.g., to test an existing vaccine, test a new vaccine, explore correlates of protection against certain endpoints, assess the degree of immunity conferred by wild virus, etc.);
- Discussing technical concerns that need to be addressed to develop a robust protocol design and plan for effective implementation and expected outcome;
- Considering the issues and impact that human challenge studies may have on acceptance and uptake of COVID-19 vaccines that are ready for roll-out;
- Discussing the potential role for human challenge studies to play in evaluating the second and third generation of COVID-19 vaccines;
- Reviewing whether there are new additions to the therapeutics armamentarium that could serve as a reliable “rescue treatment”;
- Discussing the advantages and disadvantages of using different GMP virus batches;
- Identifying areas that could be harmonized across STAGE 1 COVID-19 human challenge models;
- Discussing recommendations and next steps.
Overview/Background

Currently, there are several types of vaccine candidates in development that are demonstrating encouraging proof of principle in terms of good safety profile and efficacy, and are being tracked by the WHO landscape, in collaboration with global partners. In November 2020, some research groups announced that they were planning to undertake volunteer challenge studies to develop and utilize a COVID-19 challenge model. There was a need to understand the current situation in terms of questions that the investigators were going to address using their models and how closely the models comply with specific technical guidelines contained within the WHO document on COVID-19 challenge models. One specific important question was to shape information on whether or not there is or will imminently exist effective “rescue treatments”. This will impact the study design, implementation and outcome of challenge studies, for which WHO can deliver guidance.

- Human challenge studies are used as a tool to establish pathogenicity, identify host risk factors, characterize immune responses and correlates of protection, assess infection and pathogenesis dynamics, and provide preliminary evidence on vaccine efficacy that can guide further vaccine development.

- Whereas several publications highlight the potential benefits that human challenge studies can provide, there are other experts with considerable experience in human challenge models who bring to light several factors that warrant caution and advise against implementing challenge studies with SARS-CoV-2 infection. Such factors include the potential for severe clinical illness in young adults including complications such as thromboembolic events, high transmissibility of the pathogen and lack of a reliable “rescue treatment” to arrest progress of illness from mild/moderate to serious and potentially life-threatening.

- Although there has been progress with extensive research for “rescue treatments”, the development of GMP challenge viruses, formation of collaborative partnerships and the availability of three highly efficacious COVID-19 vaccines developed by Moderna, Pfizer/BioNTech, Oxford University/AstraZenena, all of which validate the opportunity to conduct challenge studies, the persistence of the anti-vaccine groups continue to disseminate negative information undermining public confidence and driving hesitancy which is a concern that the scientific/public health community have an obligation to be mindful of and consider in order to ensure the publics’ perception remains positive.

- When considering the timing of initiating human challenge studies with SARS-CoV-2, it is critical to account for the current regional and global strategies being implemented to control COVID-19 and acknowledge a broad perspective when prioritizing the scientific, clinical and epidemiological questions that can only be addressed through challenge studies. This will minimize the ethical concerns and impact on vaccine hesitancy when developing the study models and mitigate the potential negative outcomes that can be detrimental to undermining the global response to COVID-19.

- Based on available evidence, there are no active nor fully effective “rescue treatments” to reliably prevent the progression of COVID-19 from mild to severe. There are potential rescue
strategies in development for targeting inhibition of viral replication, receptor and enzyme blocking, antagonizing specific mediators and attenuating consequences. However, the ongoing trials and evaluations are too early to indicate their efficacy.

Session one on the discussion of challenge study plans for COVID-19:

This session focused on gathering intelligence from three investigation groups that shared high-level overview of their study protocols enabling discussion around their approach and technical matters regarding characterization of the challenge stock, titration, selection of volunteers, de-risking problems, measuring of vaccine performance, containment facilities etc.

- In general, all three groups are planning to conduct human challenge studies with low risk healthy individuals (aged 18-30) to initially determine through dose escalation the target dose of challenge agent that will elicit an asymptomatic level of illness. This will enable subsequent investigations into understanding the immune response to asymptomatic infection, differences in infectivity (by dose, virus strain and human host), kinetics of clinical signs and symptoms should they develop (despite subclinical infection being the intended goal), and correlates of protection against asymptomatic SARS-CoV-2 infection in order to assess the efficacy of different vaccines (novel candidates, formulations and regimens). These models propose to use viral shedding as a surrogate for potential further person-to-person transmission of SARS-CoV-2 in immune (vaccinated or recovered volunteers) versus non-immune (unvaccinated, serologically-negative persons with no history of COVID-19). This type of challenge model would also provide an opportunity to evaluate therapeutics (against asymptomatic shedding) and novel diagnostic tests.

- A consortium has been established among Imperial College London, the Royal Free Hospital, and the hVIVO company, supported by the UK Vaccines taskforce, for the implementation of COVID-19 human challenge studies. The UK will be working with scientific and specialist groups, including the Health Research Authority (HRA) and regulators to ensure the ethical safety of volunteers are prioritized and maintained.

- The Oxford group reported that they will be conducting their study in parallel with Imperial London College and intend to use their human challenge model to understand the definition of protective immunity focusing on susceptibility to re-infection through people previously infected with SARS-CoV-2 and investigate how they are resistant to re-infection, compared to a naïve control group. The study will be using the same GMP virus stock, protocol endpoints and DSMB as the Imperial London College group, thus allowing direct comparison of data across the two studies.

- The Netherlands GMP virus stock (using a virus that contains a DG14G mutation and grown in GMP vero cells) was originally extracted from a COVID-19 patient, characterized by Next Generation Sequencing (NGS) and will be made available to other centers at no cost.

- The UK GMP virus stock has been developed based on:
  o Collecting viruses from patients in hospitals to ensure the strain is equivalent to the endemic and circulating strain in the UK and
- Ensuring the virus has the dominant D614G mutation strain (relevant in early December 2020).
- Growing clinical samples in both qualified vero cell lines (which is in accordance with GMP production of biological products) and using human airway epithelial cells as the closest surrogate of replication in humans.

Various tests have been made to ensure viral stock sterility, mycoplasma screening, using next generation sequencing (NGS) to check and monitor for mutations during the passaging process.

- Although plaque purification of the virus is traditionally used to minimize contamination risks, NGS and sophisticated molecular techniques were used to mitigate these risks over selecting an arbitrary plaque, which may not reflect the naturally occurring COVID-19 strain. There have been no significant changes observed through the passaging method used to develop the UK GMP virus lot.

- In alignment with the WHO guidance, only healthy individuals will be enrolled and virus dosing will start with an inoculum titre of 10^1 TCID50. However, there is a concern that at such a low targeted inoculum dose there may be quantities of non-infectious virus in the inoculum.

- All studies will evaluate the pathogenicity of the GMP virus stock in animal models, characterizing the dose range and comparing the response to literature and other wild type strains.

- The standard procedure for inoculation into the upper respiratory tract will involve using a pipette, the Imperial study intends to deliver the virus stock at the smallest volume possible (200 ul) at equal amounts into each nostril (100ul per nostril 30 seconds apart) while the neck is hyper extended, followed by lying on the back for 20 mins.

- Studies will be conducted in specialized isolation facility wards where the volunteers will be contained for safety, protection and close monitoring, with highly trained health professionals following PPE/hospital guidelines, appropriate Infection, Prevention and Control (IPC) and the specialized facilities will be situated close to a hospital with infectious disease units in case of medical emergencies and ICU requirements.

- There will be no compulsory containment imposed (in Holland this is not mandatory by law), so if a volunteer decides to discharge themselves, they will be connected to their local public health authority for follow up of contact tracing. Prior to discharge, the volunteer would be offered treatment, education and counselling to ensure appropriate self-isolation is maintained during the infectious period.

- It was suggested during discussion that field trials may be an appropriate alternative to a challenge study for gathering information on whether a vaccine that Emergency Use Authorization has can diminish the occurrence of subclinical SARS-CoV-2 infection. Such randomized, placebo-controlled could be conducted as field studies among university students that represent the same age group who are healthy low-risk individuals and are not target populations for early implementation of vaccine, so that use of a placebo group is
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ethically appropriate. Enrolled health young adults would be followed weekly with sensitive and specific PCR tests (for several months) to detect and compare the occurrence of asymptomatic SARS-CoV-2 infections among vaccinated versus placebo recipients in a natural setting of high-level community transmission. This model could assess whether vaccines prevent asymptomatic infection and can be easily implemented with the capacity to recruit several thousand students.

Session two on the discussion on ethical considerations:

The second session provided an overview of the ethical concerns and sensitivities regarding COVID-19 human challenge studies, focusing on the impact it would have on public perception, particularly among vulnerable communities concerning the acceptance and uptake of vaccination as an intervention to effectively control the pandemic.

- Human challenge studies are highly complex and can lead to misinterpretation and confusion among the public, resulting in increased fear, scepticism, hesitancy and reduced acceptance of novel COVID-19 vaccines, particularly as the current environment is extremely volatile due to the politicization of the pandemic and the historical association of abuse with human subjects, in particular among different ethnicities and marginalized communities.

- As challenge trials are associated with “inoculation of the virus” into a volunteer this can instigate a false impression resulting in increased public confusion, misunderstanding and mistrust due to the inability to distinguish between vaccination and challenge studies. The expectation is that the media coverage would cause further damage to an already fragile situation by fuelling the lack of public confidence in the government and pharmaceutical industry.

- It is essential to empower the general public in a variety of ways by adopting multiple communication methods through open dialogue and sharing of data by translating scientific terminology into digestible language for providers and the public. The current terminology used to describe interventions and products related to Emergency Use Authorization include “experimental”, “accelerated approval” and “off-label” creates negative emotions of being suspicious, risky, over controlling, desperate and urgent. Use of these terms will have implications worldwide as vaccine challenge trials take place concomitant with the roll-out of approved vaccines.

- From an African perspective, there have been multiple human challenge studies conducted for various endemic diseases that are scientifically valid. However, in some instances this has resulted in fear and mistrust at the community level, potentially leading to a negative impact on public health. The LMIC context needs to be taken into account as this is a different setting to HICs. In LMICs the ethics and needs should consider religion, culture, displaced communities, ethnicity, socioeconomic background, payment, political leaders, healthcare workers at all levels of the health system, and vulnerable and marginalized populations that inevitably suffer the most from the disease due to inequitable access to vaccines and other interventions. Communities require full, transparent and comprehensible communication especially in rural
settings where traditional healers or religious leaders may control the information flow of entire communities.

- When planning for human challenge studies, it is important to focus on the top priority for stopping the pandemic, as there is pressure to understand the safety and efficacy of new promising vaccines, the timing for initiating challenge studies should be considered as COVID-19 is highly politicized and question whether such studies need to be conducted in the African continent where the health system is already fragile.

- Issue of public trust is the core aim of research ethics and central to the success of COVID-19 vaccination programmes. With the current environment of hesitancy towards COVID-19 vaccination, there are two scenarios to be cognizant of, (1) if there is news of serious injury or death of a healthy volunteer in a human challenge study, even if SARS-CoV-2 is the cause, the vaccine will be blamed, and (2) if there is a containment breach at a facility where a human challenge study is being conducted, or the premature departure from the challenge study of a study participant, leading to an outbreak in the community, scientists will be blamed, even if the transmission was due to the faulty behaviour of an individual study participant. This underlines the WHO’s recommendation for compulsory isolation of participants in COVID-19 challenge studies until all are no longer infectious.

Considerations /Summary

The Advisory Group agrees that there are some important issues and questions to address which require further deliberation, including the concern for a reliable “rescue treatment” for human challenge studies. There is a need to contemplate the ethical, technical and logistical implications for implementation of suitable containment facilities with challenge volunteers, which can be discussed in parallel conversations on the study design. It is worthwhile considering the appropriate timeliness for initiating human challenge studies. Perhaps new data can provide important information to guide the study plans of investigators considering the initiation of challenge studies. Technical discussions will continue to support the research groups towards ensuring the quality of challenge studies in terms of standards, norms and harmonization of the study protocols. It is critical to engage with civil society networks to gather their considerations and concerns to ensure a balanced dialogue regarding human challenge studies.

Proposed next steps

- WHO will organize an open forum call with technical experts to discuss the protocols of the human challenge studies in detail;
- WHO will reconvene the Advisory Group in Q1 2021 to review the situation for initiating and establishing COVID-19 human challenge studies in order to provide advice and support in making informed decisions.