Viewpoint of a WHO Advisory Group Tasked to Consider Establishing a Closely-monitored Challenge Model of Coronavirus Disease 2019 (COVID-19) in Healthy Volunteers

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WHO convened an Advisory Group (AG) to consider the feasibility, potential value, and limitations of establishing a closely-monitored challenge model of experimental severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19) in healthy adult volunteers. The AG included experts in design, establishment, and performance of challenges. This report summarizes issues that render a COVID-19 model daunting to establish (the potential of SARS-CoV-2 to cause severe/fatal illness, its high transmissibility, and lack of a “rescue treatment” to prevent progression from mild/moderate to severe clinical illness) and it proffers prudent strategies for stepwise model development, challenge virus selection, guidelines for manufacturing challenge doses, and ways to contain SARS-CoV-2 and prevent transmission to household/community contacts. A COVID-19 model could demonstrate protection against virus shedding and/or illness induced by prior SARS-CoV-2 challenge or vaccination. A limitation of the model is that vaccine efficacy in experimentally challenged healthy young adults cannot per se be extrapolated to predict efficacy in elderly/high-risk adults.

Keywords. COVID-19; SARS-CoV-2; challenge model; experimental challenge; adult volunteers.

Recognizing the helpful role that experimental challenge studies in healthy adult volunteers have played in the development of certain vaccines [1–15], some researchers have advocated undertaking such studies with virulent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [16–18]. However, several factors warrant that special caution must be taken when working with SARS-CoV-2, including the severity of coronavirus disease 2019 (COVID-19), as evidenced by its high case-fatality risk in certain sub-populations (elderly, obese, diabetics, hosts with pulmonary and cardiac disease); severe disease requiring ventilator support, thromboembolic events, and deaths (albeit relatively uncommon) also occur in young adults (although risk factors for these outcomes remain uncharacterized); the high transmissibility of SARS-CoV-2 from person-to-person directly by respiratory droplets and at further distances by airborne droplet nuclei [19]; SARS-CoV-2’s ability to remain viable on fomites for hours; since the pandemic began, multiple new clinical presentations of COVID-19 have been described. Finally, as of mid-July 2020, a reliable “rescue treatment” has yet to be identified that can predictably arrest the progression from mild/moderate COVID-19 to serious, life-threatening illness. Understandably, among experienced challenge model investigators the topic of undertaking...
challenge studies with virulent SARS-CoV-2 has generated discussion about whether the conditions can be assured to perform challenge studies safely, and what the priority goals should be for such studies.

Taking into account the cited reasons for caution, if conditions were deemed suitable to undertake development of a closely-monitored SARS-CoV-2 challenge model in healthy young adult volunteers, important information could accrue, such as determining whether an initial challenge infection confers significant protection against a subsequent challenge with homologous virus (and whether infection-derived protection extends to other virus clades); identifying potential immunologic correlates of protection against illness and virus shedding that might accompany recovery from a prior SARS-CoV-2 experimental challenge; estimating the efficacy of vaccine candidates based on different vaccine platforms (mRNA, DNA, protein, viral-vectored, inactivated whole virus, live attenuated virus) in preventing COVID-19 illness and SARS-CoV-2 shedding.

In April 2020, the WHO convened a multidisciplinary, multicontinent group to discuss the concept of volunteer challenges with SARS-CoV-2 from different perspectives. This Advisory Group (AG) included experts in design and performance of many types of volunteer challenge studies; SARS-CoV-2 virology; measurement of human immune responses to SARS-CoV-2 and other pathogens; clinical management of COVID-19 in diverse settings; regulatory considerations associated with testing and emergency prelicensure use of vaccines and with larger-scale postlicensure deployment; and Good Manufacturing Practices (GMP) manufacture of viruses. The AG was divided into four subgroups to address: Clinical Trials Issues, Challenge Virus Strain Issues, Measurement of Immune Responses, and Detection of SARS-CoV-2 in Clinical Specimens. The AG agreed to follow the evaluations of potential treatments aiming to interrupt the progression of COVID-19 in a manner that is not missed. To address the high transmissibility of SARS-CoV-2 and how challenges might proceed when there is little or no ongoing transmission in a community, the AG recommended that early (STAGE 1) dose-escalation studies should be performed in High-Level Isolation Units (HLIU) that certify rigorous physical and biological containment [21–23], while assuring facile access/transport to intensive care for volunteers, if necessary. A protocol synopsis incorporating these concepts is provided in Supplementary Material.

To protect household and community contacts of challenged volunteers, the AG recommends that these studies, in coordination with local public health and civil authorities, be performed under legal quarantine (health authority-issued state of compulsory isolation) [24, 25]. This is analogous to the compulsory isolation in healthcare facilities of patients with Ebola, MERS, or extensively drug-resistant tuberculosis, until they are no longer infectious, as has occurred under revised isolation/quarantine laws enacted in many countries (and state and municipal jurisdictions therein) in recent years. The precedent for quarantine/compulsory isolation during volunteer challenges was set during early cholera challenges performed with community volunteers at the University of Maryland’s Center for Vaccine Development in Baltimore, MD, in the mid-1970s [1, 26]. Following this approach, a volunteer who wishes to leave the study after it begins, as is their right, could do so (no more study procedures) but they would not be allowed to leave the Isolation Unit until they were no longer infectious. For quarantine/compulsory isolation studies, volunteers must be stringently screened to enroll only those deemed diligent and committed and who clearly understand this concept. Compulsory isolation/quarantine is distinct from housing volunteers in a high containment facility but allowing them to leave the study prematurely if they agree to continuing follow-up thereafter [27].

To minimize the chance of virus reaching the lungs, the AG recommends that the virus inoculum be instilled into the nostrils of the volunteer (0.5 mL per nostril) using a pipette or a well-characterized nasal spray device that can assure that particle size always exceeds 5 microns in diameter. The AG concluded that initially the steps of dose preparation and intranasal administration of challenge virus to volunteers should be performed in a HLIU with rigorous safeguards against droplet and droplet nuclei airborne transmission to minimize the risk of virus spread to research staff and the community. The AG proposes that ~1 x 10^2, ~1 x 10^3, and ~1 x 10^4 median tissue culture infectious doses (TCID_50) should be the initial dose levels to be investigated in different groups of volunteers in dose-escalation fashion to achieve a 70% clinical attack risk for mild upper respiratory illness, accompanied by shedding of SARS-CoV-2. There is no way to predict whether multiple passages in tissue culture during manufacture will have attenuated the challenge viruses or whether, in contrast, illness in some volunteers may become severe, an outcome to be avoided. A Data
Safety Monitoring Board should review safety and shedding data from all volunteers at each dose level and advise of their decision to recommend, or not, escalation to the next higher dose. Volunteers will remain on the HLIU until they have exceeded the usual upper range of incubation (~14 days) and have ceased shedding virus (confirmed by RT-PCR) for 3 consecutive days. If stepwise dose-escalation studies investigating different SARS-CoV-2 clades yield a safe model, STAGE 2 studies involving larger numbers of volunteers could proceed, such as challenge/re-challenge studies to assess the protection against illness and virus shedding conferred by primary SARS-CoV-2 infection and randomized, placebo-controlled assessments of vaccine-induced protection against illness and virus shedding.

Challenged volunteers should be followed for at least 12 months to rule out late adverse consequences.

Figure 1. Discussion at the initial videoconference meeting of the Advisory Group (AG) on April 30, 2020 provides an overview of some the strategic steps and decision trees that the AG agreed to grapple with in considering the feasibility of establishing a closely-monitored experimental challenge model of SARS-CoV-2 virus infection and COVID-19 in volunteers. The first was to select whether to begin with a putatively attenuated SARS-CoV-2 strain or with virulent SARS-CoV-2. Since the AG was unaware of an attenuated strain having progressed to where it could be administered in clinical trials, discussion thereafter focused on issues associated with challenge of volunteers with virulent SARS-CoV-2. Several AG members were concerned that clinical studies should not begin until there was a proven “rescue treatment” efficacious in reliably arresting the progression of COVID-19 illness from a mild/moderate status to severe COVID-19. While that “gate” remained in the background, the AG agreed to follow the progress of therapeutic regimens that were in controlled clinical trials to identify a “rescue treatment.” During the months that the AG was active (until early June 2020), remdesivir was reported to diminish the days of hospitalization of severe COVID-19 cases and subsequently dexamethasone was shown to diminish mortality of hospitalized patients. However, neither of these constitutes a “rescue treatment” defined as a specific treatment capable of reliably interrupting the progression of mild/moderate COVID-19 to severe illness. The AG discussed two main uses for a SARS-CoV-2 challenge model once the initial dose/escalation was completed and an acceptable, predictable challenge dose was identified that could be used to answer specific questions. One was re-challenge of a group of volunteers who shed SARS-CoV-2 and developed mild illness on an initial challenge ~6 weeks earlier, along with a new group of naive control volunteers. Such studies could explore whether the immune responses elicited in the re-challenged “veteran” volunteers may be reflective of protection, as evidenced by diminished shedding of SARS-CoV-2 and prevention of clinical COVID-19 upon re-challenge. If substantial protection was observed it would be possible to look for an immune response (eg, IgG anti-spike receptor binding domain antibodies, or neutralizing antibodies) that correlated with protection. The other main use of the model, once established, would be to assess preliminarily the efficacy of COVID-19 vaccines based on somewhat different concepts. Evidence of protection of subjects given COVID-19 vaccines against challenge with virulent SARS-CoV-2 could set the stage for identifying correlates of protection, as the serum and mucosal antibodies and cell-mediated immune response measurements would be available from pre- and post-vaccination and from immediately pre- and post-challenge specimens. If significant protection was observed against both clinical endpoints and against viral shedding, this information would contribute to the development of efficacious COVID-19 vaccines by helping to elucidate how they function, based on data generated under closely monitored experimental conditions. Abbreviations: COVID-19, coronavirus disease 2019; EUA, emergency use authorization; IgG, immunoglobulin G; RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine efficacy.

SELECTING CHALLENGE VIRUS STRAINS AND BIOSAFETY LEVEL-3 (BSL-3) GMP MANUFACTURERS

In case virus growth or yields differ, the AG concluded that 2 separate isolates should be selected from clade B1 (circulating in Europe and the Americas) and 2 from clade A (original outbreak strain in China) to be sent to manufacturer(s) to prepare Good Manufacturing Practices (GMP) batches. B1 lineage has a mutation in the spike protein (D614G) that may be important, since these variants exhibit increased attachment to the ACE-2 receptor and may manifest enhanced transmissibility. Viruses
can be selected that harbor the D614G but few other mutations. A list of isolates was assembled to provide potential challenge viruses. Although documenting the clinical history of patients whose virus isolates are selected is not a regulatory requirement, some AG members opined that, ideally, challenge isolates should be obtained from a subject with nonfatal COVID-19 who did not have known risk factors. Using a virus engineered by reverse genetics was also discussed, since a genetic “bar code” could be inserted to tag this virus. While not an immediate option, this should be considered a back-up where use of a genetically modified organism (“GMO”) would not evoke regulatory constraints [28].

Each candidate isolate should undergo 3 rounds of plaque purification in a validated cell line in a BSL-3 facility; 5–10 passages of virus may be necessary to obtain adequate yields. Challenge strains should undergo Next Generation Sequencing (NGS) at the start and end of manufacturing to detect mutations. Some researchers have observed a deletion that removes the furin cleavage site from the spike protein following culture in Vero cells.

Two viruses (at least one clade B1) that provide good yields should be selected for fill and finish of the challenge material batches to prepare clinical study-ready vials containing challenge virus in frozen liquid at ~10^2, ~10^3, and ~10^4 TCID₅₀ dose levels. The AG and prospective manufacturers concluded that the preferred formulation and safest presentation would be frozen liquid containing virus within screw-top vials. Lysophosphatidyl ethanolamine was deemed undesirable, as they would require a reconstitution step with diluent that would increase biocontainment risk. To assure there is no substantial loss of virus viability/infectivity over time, vials containing the final virus “drug product” must undergo periodic testing to monitor virus titer (TCID₅₀ or PFU). An experienced courier service confirmed the details needed to transport vials of SARS-CoV-2 to challenge study sites.

**MEASUREMENTS OF IMMUNE RESPONSES AND VIRUS SHEDDING**

The AG discussed the importance of measuring a wide array of innate, adaptive humoral (serum and mucosal), and cell-mediated immune responses to SARS-CoV-2 (Table 1). Measurements in larger STAGE 2 studies, such as challenge/re-challenge studies and preliminary assessments of vaccines, may allow identification of immunologic correlates of protection. Methods to monitor virus shedding were also proposed.

**ABILITY TO EXTRAPOLATE VACCINE EFFICACY IN YOUNG ADULTS TO VACCINE PERFORMANCE IN THE ELDERLY**

Experience with influenza vaccines instructs that it is problematic to extrapolate vaccine efficacy results from young adults to estimate vaccine efficacy/effectiveness in elderly persons. Immunosenescence renders influenza vaccines less immunogenic and less protective in the elderly [29]. To overcome this, vaccines for the elderly have been developed that include 4-fold higher doses of hemagglutinin, or potent adjuvants. Since several COVID-19 vaccine candidates in clinical trials incorporate new technologies/platforms for which licensed vaccines do not yet exist, there is no basis to predict their efficacy in elderly versus younger adults, prior to field trial evaluation.

**CAN EVIDENCE OF VACCINE EFFICACY IN YOUNG ADULTS IN A CHALLENGE STUDY ACCELERATE ACHIEVING EMERGENCY USE AUTHORIZATION BY REGULATORY AGENCIES FOR BROADER PUBLIC HEALTH DEPLOYMENT OF THE VACCINE?**

The AG sought to separate the vaccine development paradigm classically followed in development of vaccines to prevent endemic infections versus vaccines against Public Health Emergency of International Concern (PHEIC) pathogens. Classical paradigm vaccine candidates are evaluated step-wise through Phase 1, Phase 2, and Phase 3 clinical trials to establish their safety, immunogenicity, and efficacy with a final formulation that can be consistently manufactured [30]. This undertaking typically requires >10 years to bring a vaccine to licensure. Related issues include assuring an adequate supply of vaccine, financing to procure doses for target populations, and a delivery strategy and infrastructure to vaccinate targeted populations. Development of vaccines against PHEIC pathogens requires a greatly accelerated process that overlaps phases and necessitates enhanced coordination among stakeholders.

Heretofore, the paradigm for highly accelerated testing of candidate PHEIC vaccines in clinical trials to show safety, immunogenicity, and efficacy leading to prelicensure emergency use was set during the West African Ebola epidemic with the VSV-vectored Ebola vaccine expressing Ebolavirus Zaire glycoprotein (rVSV∆G-ZEBOV-GP). A WHO-led investigator consortium accelerated development of what is now the licensed Ebolavirus vaccine Ervebo™ (Merck Vaccines) from the clinical experience of a single vaccinated subject (August 2014) to documentation by June 2015 of the efficacy of that vaccine in a cluster-randomized controlled Phase 3 trial, a period of only 10 months [31]. The time from Phase 1 and 2 trial results that established dose-level and immunogenicity of rVSV∆G-ZEBOV-GP [32, 33], until initiation of the field trial to assess efficacy of the vaccine in Guinea was only 2 months [31]. This included preparing the trial site in Guinea, and training clinical, field, and laboratory staff in Good Clinical Practices (GCP) [34], arranging trial monitoring [34], and installing on-site data management. The field trial provided evidence of efficacy within 4 months [31]. Importantly, rVSV∆G-ZEBOV-GP's
<table>
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<tr>
<th>Immune effector</th>
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<th>Antigen (source)</th>
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<td>Spike or S1 protein or receptor binding domain (RBD)</td>
<td>Binding</td>
<td>Baseline, days 7, 14, 21, and 28</td>
<td>IgG, IgM and IgA ELISA; IgG subclasses</td>
<td>Binding antibody; subclasses</td>
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<td>Serum/plasma</td>
<td>Live (infectious) virus</td>
<td>Neutralizing Ab</td>
<td>Baseline, days 7, 14, 21, and 28</td>
<td>Neutralizing Ab</td>
<td>Requires BSL3 containment; gold standard</td>
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<td>Serum/plasma</td>
<td>Pseudovirus expressing SARS-CoV-2 spike protein</td>
<td>Neutralization of virus entry</td>
<td>Baseline, days 7, 14, 21, and 28</td>
<td>Neutralizing Ab</td>
<td>Must be accompanied by neutralization assays using infectious virus</td>
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<td>Neutralizing Ab</td>
<td>Must be accompanied by neutralization assays using infectious virus</td>
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<td>SARS-CoV-2 peptides or inactivated virus</td>
<td>cTfh; Activated CD8+ T cells; B cells: Antibody secreting cells (ASC); memory B cells</td>
<td>Baseline, days 7, 14, and 28</td>
<td>Flow cytometry</td>
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<td>Baseline and every other day</td>
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Abbreviations: Ab, antibody; ACE, angiotensin-converting enzyme; BSL, biosafety level; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; ELISPOT, enzyme-linked immunospot assay; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IL, interleukin; N/A, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sVNT, surrogate virus neutralization test.
efficacy trial ensued in a low-income country without a re-
search infrastructure or clinical investigators and staff experi-
enced in GCP [34]. COVID-19 vaccines, in contrast, can be 
assessed with experienced clinical and laboratory research per-
sonnel in high-income and low-to-middle-income, countries 
(LMICs).

With efficacy demonstrated, rVSVΔG-ZEBOV-GP was used 
as an investigational product under monitored emergency use 
to control an Ebola outbreak in Southeast Guinea (2016) [35], 
and then in Democratic Republic of the Congo (2018) [36]. 
In 2019 the US Food and Drug Administration and European 
Medicines Agency licensed Ervebo™.

PUBLIC PERCEPTION

The AG discussed the public perception of volunteer challenge 
studies with SARS-CoV-2. Potential volunteers in the USA and 
other countries are signing up to a website promoting chal-
lenge studies. However, in both high-income and LMICs, seg-
ments of the population are already hesitant about some of the 
safest, most important, vaccines in public health (eg, measles 
vaccine) and many have vowed to decline immunization with 
a COVID-19 vaccine [37–39]. Several AG members cautioned 
that challenge studies undertaken in the absence of an effective 
“rescue treatment” could incite the antivaccine movement and 
discourage persons with hesitancy toward vaccines from being 
vaccinated [40], particularly if there is an impression that chal-
lenge studies were intended to be a “shortcut.” The public trust 
needed to achieve high vaccination coverage with COVID-19 
vaccines could be undermined if there was a highly-publicized 
serious adverse event in a challenged volunteer [40].

AG RECOMMENDATIONS

1. Clinical trials to establish a model of COVID-19 should 
be divided into an incremental strategy in which STAGE 1 
encompasses early studies that explore the model through 
first-in-human, stepwise, dose-escalation studies with 3 dif-
ferent dose levels and close monitoring of the volunteers to 
reveal the clinical response and the virus shedding pattern. 
Subsequent STAGE 2 studies involving larger numbers of 
volunteers would address questions such as the level of pro-
tection conferred by infection-derived immunity and the 
preliminary efficacy of different vaccines.

2. Volunteers should be restricted to healthy individuals 
18–25 years of age, as these have a much lower case-fatality 
risk than older COVID-19 patients.

3. To address the high transmissibility of SARS-CoV-2 and the 
need to administer the virus to volunteers intranasally in a 
high level of containment that minimizes consequences of 
droplet and aerosol generation, and to protect clinical re-
search and ancillary staff, STAGE 1 studies to establish the 
model should be performed in HLIUs (ie, high-level clinical 
containment facilities).

4. To allow challenge studies to proceed during periods when 
there is little or no COVID-19 in the community, and to pro-
tect household contacts and community contacts of chal-
lened volunteers, the HLIU for STAGE 1 studies should be 
placed under legal quarantine/compulsory isolation during 
the period of the study. If so, a participating volunteer who 
decides to “leave the study,” which is their right, will never-
theless not be allowed to leave the quarantined Isolation Unit 
until they are no longer infectious. This will require close 
coordination with local public health and civil authorities 
where the HLIU is located. The precedent for establishing 
quarantine was set during early cholera challenge studies in 
community volunteers performed in USA in the mid-1970s.

5. The AG recommends selecting 2 isolates from Clade B1 and 2 
from Clade A to send to a GMP manufacturer to have batches 
of virus prepared in appropriate formulation and presenta-
for use in a SARS-CoV-2 challenge model.

6. The 4 selected viruses should be sent to a GMP manufac-
turer with BSL-3 capability where the viruses would be 
plaque-purified thrice in qualified cells and sequenced by 
Next Generation Sequencing before and after manufacture; 
2 GMP batches (at least one clade B1) should be finished and 
filled to produce vials of the frozen liquid formulation at the 
three dose levels. The virus titer stability of these challenge 
products should be monitored over time.

7. Dose levels proposed for the STAGE 1 first-in-human, step-
wise, dose-escalation studies of each virus are ~10², ~10³, and 
~10⁴ TCID₅₀. If necessary, a 10-fold higher dose level, ~10⁵ 
TCID₅₀, may be prepared.

8. Various therapeutic regimens for COVID-19 that are being 
tested in large randomized, controlled clinical trials world-
wide should be closely followed to see if an intervention 
emerges that might serve as a credible “rescue treatment” for 
SARS-CoV-2 volunteer challenge studies to reliably interrupt 
the progression from mild to severe COVID-19.

Whereas the votes of the AG members on the above-
mentioned 8 technical recommendations were either unani-
ous or near unanimous, the AG was split approximately in 
half in voting their opinions on the 3 questions shown below.

1. Should challenge studies begin if properly formulated chal-
lenge viruses in the 3 desired dose levels become available in 
the next few months but there is not yet a recognized “rescue 
treatment” to arrest the progression of COVID-19 from 
mild/moderate to severe illness? (8 voted “to begin” without 
such treatment, 11 voted “not to begin”).

2. Will efficacy results in young adults in a challenge model pre-
dict efficacy in elderly and high-risk adults? (7 opined the 
model would and 12 declared it would not).
3. Would challenges in young adult volunteers accelerate the timeline for progressing a vaccine to achieve emergency use authorization for deployment in segments of the population suffering high mortality (elderly, diabetics), compared to the performance of large-scale randomized, controlled field trials of efficacy that included high-risk target populations? (9 opined challenges would accelerate; 9 thought field trials would be faster; 1 abstained).

Supplementary Data
Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes
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