Biologicals 67 (2020) 69–74

Contents lists available at ScienceDirect

Biologicals

journal homepage: www.elsevier.com/locate/biologicals

SARS-CoV-2 controlled human infection models: Ethics, challenge agent production and regulatory issues

Marc Baay [a], Pieter Neels [b,*]

[a] P95 Epidemiology & Pharmacovigilance, Leuven, Belgium
[b] International Alliance for Biological Standardization – IABS, Geneva, Switzerland

ARTICLE INFO

Keywords:
SARS-CoV-2
Controlled human infection models
Ethics
CMC

ABSTRACT

This second International Alliance for Biological Standardization COVID-19 webinar brought together a broad range of international stakeholders, including academia, regulators, funders and industry, with a considerable participation from low- and middle-income countries, to discuss the use of controlled human infection models to accelerate development and market authorization assessment of a vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

1. Introduction

The International Alliance for Biological Standardization (IABS[1], https://www.iabs.org) is devoted to the scientific and medical advancement of biologicals, by facilitating communication among those who develop, produce and regulate biological products for human and animal health. Towards this end, IABS previously organized a webinar on COVID-19 to provide open access information on virology, epidemiology, immunology and vaccine development to a broad range of stakeholders from all continents [1]. The second webinar, reported on here, was devoted to the use of controlled human infection models (CHIM) to accelerate development and market authorization assessment of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It consisted of four brief presentations to set the stage, followed by three panel discussions on ethics, challenge agent production and quality control issues (CMC) and regulatory issues, with ample time for discussion between panelists and participants. The meeting was organized under the Chatham House Rule (https://www.chathamhouse.org), which means that participants are free to use the information received, but neither the identity nor the affiliation of the speaker(s), nor that of any other participant, may be revealed.

1.1. The human challenge agent

Challenge agents should be representative of what is seen in the field, to be able to provide efficacy data relevant to candidate vaccines (or other prophylactic or therapeutic interventions) at an early stage. Requirements for challenge studies are: 1) susceptible volunteers in the general population, preferably in high numbers to quickly populate the trials; 2) a high and consistent attack rate of the challenge agent, with low intermittent shedding, as this will reduce the number of participants needed; and 3) a high number of volunteers with measurable morbidity, to be able to determine efficacy.

When designing a CHIM study for vaccine development, the antigenic relevance of the challenge agent is highly important; vaccines can be developed in many ways, with differing genetic complexity and replication potential. The most successful vaccines have used strains or carriers which were capable of replication. Furthermore, using the whole virus may allow the generation of cross-protective antibodies. The challenge agent seed stock should represent the circulating antigenic strains and next generation sequencing can be used to investigate the relevance of the chosen isolate [2].

Previous research on human coronavirus OC43 (HCoV-OC43) has shown that substitution mutations in the virus' DNA (or RNA) may cause the virus to escape from monoclonal antibodies, and the majority of such substitutions is located in the major antigen spike (S) gene S1 subunit

* Corresponding author.
E-mail addresses: marc.baay@p-95.com (M. Baay), Pieter.neels@vaccine-advice.be (P. Neels).

[1] BSL - Biosafety level; CHIM - controlled human infection model; CoV – coronavirus; HCT - Human challenge trials; HIC - high-income countries; IABS – International Alliance for Biological Standardization; LMIC - low- and middle-income countries; PHEIC - Public Health Emergency of International Concern; $TCID_{50}$ - 50% tissue culture infective dose; WHO - World Health Organization.

https://doi.org/10.1016/j.biologicals.2020.08.006
Received 11 August 2020; Accepted 12 August 2020
Available online 15 August 2020

[3]. Genetic drift of the S gene is likely to be one of the mechanisms of the adaptation evolution of HCoV-OC43, and this may also be the case for SARS-CoV-2.

In the brief history of SARS-CoV-2, several SARS-CoV-2 clades have quickly developed despite the absence of pressure of antibodies generated after infection, vaccines or drugs. Therefore, the clade development must have been caused by unchanneled changes, of which one or two per month are expected to occur in mutagenic sites in the virus' DNA/RNA. Nevertheless, the antigenicity seems to be fairly well retained across the clades, although this may change with increasing pressure. So far, while antigenic drift is observed, no antigenic shifts have taken place. To ascertain seed stock diversity for the production of challenge agents for CHIMs, representatives of Clades A and B should be used, as these represent the majority of predominant circulating virus haplotypes. To ascertain antigenic relevance of selected challenge agents, deep sequencing and monoclonal binding studies can be used to provide insights into the impact of genetic changes on the antigenicity of the S protein. And finally, the preparation of Good Manufacturing Practice (GMP) seed stocks should be possible under Biosafety Level (BSL)2+, rather than BSL3, if appropriate risk assessment has taken place.

Several issues need to be resolved for challenge agent development: the source of the seed stock; the need for an.Informed Consent Form (ICF) when using patient isolates; the use of reverse genetics, genetically modified organisms, or cold-adapted virus; purification and adventitious testing; maintenance of wildtype characteristics, the best cell line to be used; the need for animal studies; and the need for pre-screening of challenge participants for serosusceptibility.

1.2. Human challenge model development plans

COVID-19 CHIMs could play a vital role in facilitating the global pandemic response to save lives and minimise the pandemic impact by: 1) expediting efficacy testing of vaccines; 2) facilitating far greater understanding of the correlates of protection; and 3) significantly enhancing the understanding of the virus-host interactions, which in turn will aid improved vaccine design. Therefore, a safe SARS-CoV-2 CHIM must be developed. A CHIM to support SARS-CoV-2 vaccine development would not deviate from the standard viral challenge models, although enhanced safety considerations are necessary, given the potentially serious consequences of the infection, and the current lack of treatment. A SARS-CoV-2 model therefore cannot be run like conventional respiratory virus challenge models, where participants resolve the disease without intervention. For a SARS-CoV-2 model, an intervention plan must be part of the study protocol to 1) minimise risk of severe disease and 2) dramatically reduce the duration of viral shedding by the participants, in order to reduce the need for extended quarantine stay and the physical and mental risks associated with long quarantine duration. Also, a rescue therapy should be included in the intervention plan, to be able to arrest the progression of COVID-19 illness from a mild or moderate severity to a severe illness. Although currently no rescue therapy is available, this is expected/hoped for in the near future, given the number of private and academic laboratories working on this around the globe. The need for a rescue therapy for a SARS-CoV-2 CHIM continues to be the source of ongoing debate in the bioethics community.

Safety is without debate the first priority when developing a CHIM; subject populations will be chosen to be those at the lowest possible risk of severe disease. Moreover, just like for any clinical study involving human subjects, challenge studies should only proceed after full ethical consideration and approval by external research ethics committees.

With so many groups worldwide focused on CHIM development, building a model is teamwork: extensive consultation should take place with infectious disease, ethics and regulatory experts and organisations throughout the process.

1.3. Human challenge studies

The impact of COVID-19 is enormous, both in the medical sense, due to morbidity and mortality, but also in the economic and cultural sense. Therefore, we need to take into account that extraordinary diseases need extraordinary solutions. Standard vaccine development has four phases. The first two are relatively short, but because the phase 3 study requires a large number of participants it generally takes much longer. Furthermore, in this phase 3 study, efficacy testing is one of the objectives. To this end, some participants in the placebo group will likely become seriously ill and may die, something which may also happen to some participants in the vaccine group. Finally, a large number of candidate vaccines is available [4], but it will be extremely difficult, if not impossible, to test all of these for efficacy, due to the ethical issue of including people in a placebo group when other vaccines have already shown efficacy. Human challenge trials may help to solve at least some of these issues. First of all, fewer subjects are needed for a CHIM than for a classic clinical trial, and the inclusion criteria for the study group can be limited to subjects at the lowest possible risk, i.e. 18-25-year-olds. Secondly, challenge trials can determine the infectious dose, starting from a very low dose. Furthermore, CHIMs can be used to compare vaccines side by side, limiting the need for placebo controls. Challenge studies could determine correlates of protection, which could be used in phase 3 studies. Finally, if the CHIM results are favorable, such a trial can help in obtaining emergency use authorization for a vaccine, to be used, e.g. in high-risk populations. Despite all these benefits of CHIMS, it is important to remember that they are a potential risk to the participants, especially with a disease which is not completely understood and for which no rescue therapy is available. Thus, even if such trials can provide sufficient information for *efficacy* testing, there will never be sufficient information for *safety* assessment, so phase 3 studies will still be needed to investigate safety in appropriate numbers of participants, to determine infrequent adverse events following immunization.

The longer we wait to set up challenge studies, the lower the chance that they can add valuable information to vaccine development, i.e. add value to regular phase 1–3 trials. The time to act is now.

1.4. The World Health Organization COVID-19 Challenge Model Advisory Group

The World Health Organization (WHO) was quick to set up an Advisory Group to consider the feasibility, potential value and limitations of establishing a closely monitored challenge model of experimental COVID-19 infection and illness in healthy young adult volunteers [5]. This Advisory Group included experts in design and performance of human volunteer challenge models, virology, immunology, clinical management, regulatory, and GMP manufacture of viruses. The Advisory Group produced a number of recommendations on which there was consensus [5]:

- An incremental STAGE 1/STAGE 2 strategy should be applied, with small STAGE 1 dose-escalation studies and larger STAGE 2 studies to investigate the level of protection and preliminary efficacy of vaccines.
- Volunteers should be restricted to healthy individuals, 18–25 years of age.
- STAGE 1 and 2 studies should be performed in High-Level Isolation Units (i.e., high-level clinical containment facilities).
- These units should be placed under legal Quarantine (Compulsory Isolation): a participating volunteer can decide to "leave" the study, but will not be allowed to leave the Quarantined Isolation Unit until the study ends
- Two isolates from Clade A and two from Clade B1 should be selected for production of four batches of virus for the CHIM.
- A GMP manufacturer with BSL-3 capability should plaque-purify the viruses three times in qualified cells, sequence by Next Generation

Sequencing before and after the plaque-purification, prepare GMP batches of two viruses, and produce vials at the requested dose levels in order to avoid dosing errors.
- Proposed dose levels for dose-escalation studies are 1×10^2 50% tissue culture infective dose $(TCID)_{50}$, 1×10^3 $TCID_{50}$, and 1×10^4 $TCID_{50}$. As necessary, a log higher dose level may have to be prepared for one or more viruses.
- Developments worldwide should be closely followed to see if any credible rescue treatment becomes available for use in a SARS-CoV-2 CHIM.

No consensus could be reached on the question of whether challenge studies should be allowed to begin if properly formulated challenge viruses in the three desired dose levels become available *before a rescue treatment is available*. Similarly, there was no agreement on the question of whether efficacy results in young adults in a challenge model will predict efficacy in elderly and high-risk adults. Finally, the group of panelists and participants was divided on whether results of volunteer challenges in young adults would accelerate the timeline for progressing a vaccine to achieve emergency use authorization and ultimately licensure for use in segments of the population suffering high mortality burden (elderly, diabetics, etc.), compared to the performance of large-scale randomized, controlled field trials of efficacy in the high risk target population [5].

In discussing the timeline needed to develop a COVID-19 vaccine from inception to having sufficient safety, immunogenicity and efficacy data and proof of consistency of manufacture to allow regulatory agencies either to license the vaccine or to issue an interim authorization for emergency use in large populations, the Advisory Group differentiated between Public Health Emergency of International Concern (PHEIC) and non-PHEIC vaccines [5].

2. Panel discussion – ethics

Human challenge studies for COVID-19 raise a number of ethical issues [6,7]. The panel discussion of this webinar focused on those issues which are currently the subject of ongoing debate within the scientific community.

2.1. Justification

How much social value might be needed to justify a SARS-CoV-2 CHIM? The primary social value of CHIMs would be to speed up vaccine development, as vaccines are needed to resume normal life. For CHIMs to have impact, the data that are produced need to feed into other studies. On the other hand, if the technology to set up CHIMs take a long time and the vaccine development proceeds at “pandemic speed”, the data from CHIMs may come too late to feed into other studies.

Human challenge trials (HCTs) will initially be performed in high-income countries (HIC), where the facilities are available to perform these studies under stringent conditions. But at what point and based on what criteria will it be decided to extend these studies to other settings? From the study of other pathogenic organisms, including malaria, helminths and other intestinal pathogens, we know that early life exposure to these may change the infected person’s response to them later in life and hence, local setting is of importance. Will this also be the case for SARS-CoV-2, to which no-one was previously exposed?

2.2. Treatment and risk minimization

Is it ethical to infect healthy young adult volunteers with COVID-19 without the possibility of a 100% effective treatment? The risks need to be quantified and compared to other viral challenge models. As can be seen from other respiratory tract CHIMs, such as RSV, influenza and CoV OC43, the risk can be reduced by selection of a study population at lowest risk, but severe complications can never be completely excluded, e.g. myocarditis, for which there is no treatment. Although these viruses have a much higher mortality rate in the elderly, the CHIMs have not been judged controversial and it was decided to proceed with them.

Risks can thus be minimized but not excluded. One risk is that rescue therapy, even if available, may not work, or may not help everyone. So, if it is judged as ethically uncontroversial to do CHIM, the presence or absence of a rescue therapy is of less importance. Nevertheless, it is always hoped that a treatment will be available before HCTs are started. This is because the impact of a serious adverse event occurring in a HCT should not be ignored. A serious adverse event would be regrettable, first and foremost for the injured participant. It could also negatively impact public perception of CHIMs and play in the cards of the vaccine hesitancy movement. The availability of a rescue therapy may prevent this.

Risks can, in addition to the above mentioned considerations, be reduced by careful challenge agent selection, careful manufacture of seed stocks, careful screening and selection of participants, and using stepped HCTs, starting with attenuated challenge agents, moving towards wildtype virus, maximizing value while securing safety. Furthermore, non-naïve participants can be included to reduce risks further, in analogy to influenza.

Determining factors for severe COVID-19 are currently unknown. The most important factor is comorbidity, which may potentially be overlooked in “healthy” individuals. Luckily, there may be a dose-response effect in severity, which in CHIM can be avoided by careful titration studies.

2.3. The ethical dimensions of participant selection criteria

Participant selection needs to be fair and minimise risks to participants. Selecting from a diverse population of healthy individuals that satisfy the inclusion criteria minimizes risks and ensures a balanced representation of the population, to the extent possible. It is clear that participation in HCTs will be limited to healthy adult volunteers, aged between 18 and 25, or maybe 30.

Proper informed consent needs to be obtained from people with an appropriate literacy level, to make sure economically vulnerable populations are not unduly induced into participation. Similarly, professional volunteerism, people who are doing it for a living, should be discouraged. One concern would be that potential volunteers don’t truly understand what they volunteer for, which should be investigated by a test of understanding. But another concern is that volunteers actively withhold information on exclusion criteria, putting them at higher risk. To avoid this, rigorous physical examinations should be performed before inclusion. On the other hand, while only including people who volunteer to do it for free may be an insurance that there is no undue inducement, it would skew the participant sample and it would be unfair to not compensate people for their time and effort invested. Fair and appropriate compensation should be the goal. People are very vocal about volunteering (1daysooner.org), as they want to do their part to respond to the pandemic and they believe this will lead to more rapid vaccine development. There is both a sense of urgency and altruism in their motivation. It would be good to further investigate what motivates these people and how their understanding is of the risks and benefits.

It was suggested that enrolment of volunteers could be restricted to, or preferentially be done among, medical students, as they have the right age and are generally better informed about the risks, or better equipped to understand the risks. However, this will depend on the local COVID-19 situation: during peaks, all staff is necessary for patient care, potentially including student doctors and nurses. Secondly, this is a vulnerable group, easily exploited in research.

Should studies only be performed in women, as men are at higher risk? Indeed, there is some evidence that males are at higher risk. In general, however, if we exclude a certain group of people from research that is supposed to protect this group, we get skewed? results that are not relevant for this group. Therefore, both men and women should be

included. Similarly, HCTs should be done on different races. Diversity is valuable, and equity should be the goal.

In how far should other potential risk factors be used in participant selection? A recent study identified a gene cluster as a genetic susceptibility locus in patients with COVID-19 with respiratory failure, and also a potential involvement of the ABO blood group system was suspected [8]. However, these associations do not indicate causality. Would participants possessing such genetic variants be outrightly excluded from CHIM studies or perhaps the study could present an opportunity to establish causality? Based on risk benefit assessment, should sites unable to conduct genetic sequencing as part of participant screening be outrightly excluded from CHIM studies regardless of the benefits to the wider community? The current WHO position on inclusion criteria is to be found in the WHO Key Criteria, saying that if data justify confidence or reasonable suspicion that any particular (sub)groups are at significantly heightened risk of serious illness (or death) resulting from infection, then they should be excluded from participation in initial studies.

If young people with no known risk factors, who understand the study, want to participate as volunteers, wouldn't it be some sort of paternalism to insist that they do not understand what they are doing? Participant selection raises the issue of soft versus hard paternalism: every study involves some justifiable soft paternalism, as you want to make sure participants understand what they sign up for. Hard paternalism, e.g. by default excluding young people to participate because it is assumed that they do not understand the risks, should be avoided.

In general, a participant has the right to withdraw from a study, however, this does not give the right to bring a risk to society. Therefore, while someone can stop providing samples to the study, it is not possible to leave quarantine as that might cause infection to third parties.

2.4. Reducing numbers of participants

As the healthy volunteers in the placebo group if a clinical vaccine trial, regardless of whether a classical study or a CHIM, have some risk of serious complications after exposure to SARS-CoV-2, the number of (placebo) volunteers should be minimized. This could be done by testing several vaccines in the same CHIM? trial, sharing the placebo arm. However, since this is unprecedented, it is unclear what issues might arise. Therefore, it would require a level of unprecedented cooperation and coordination between research groups and sites that would need to be carefully worked out from the start.

HCT in young, low-risk participants should be followed by pragmatic field studies in high risk individuals, to select and test the optimal vaccine. If it is possible through CHIM studies to determine a correlate of protection in young individuals, and determine why it protects, this response can be looked for in elderly, as shown for other vaccines. Current vaccines are generally less efficacious in elderly but will afford some level of protection.

2.5. Disease enhancement

Unfortunately, if emergency use of a vaccine is based on CHIM data, there will be insufficient data to detect disease enhancement. This could lead to vaccination of a large number of vulnerable people, who might be exposed to the wildtype virus at a later stage. By measuring and dissecting immune responses in healthy CHIM participants, including antibody responses, it can be estimated whether there is a risk for disease enhancement. However, phenomena such as disease enhancement after dengue fever vaccination are rare and can only be seen in large human trials, meaning that if it were an equally small risk after SARS-CoV-2 vaccination, this would not be detected in a CHIM.

The more we talk, the less likely it is that CHIMs can be done. Steps are being taken to prepare: production of challenge agents, discussions of legitimate challenge, identification of appropriate sites for volunteers, initially in Europe and US. If the classic vaccine trials run very quickly, providing efficacy data, HCTs may be unnecessary or less valuable, all things considered, however, until then it is prudent to continue with preparations.

3. Panel discussion – CMC (chemistry, manufacturing & controls) aspects

The discussion included CMC topics related to the production of the challenge virus, as well as related clinical topics.

3.1. Characteristics and quality attributes of the challenge agent

The sponsor, not the regulator, will propose challenge agent(s) and should provide an appropriate rationale for their choice. Additionally, all manufactured challenge agents will be reviewed by regulators according to the quality standards and requirements in the specific jurisdiction. It was noted that animal model studies using several viral strains have been useful to characterize the properties of the differing models but have not identified any substantive difference between viral isolates. Whatever the regulatory status of the challenge agent within a specific jurisdiction, a set of quality criteria need to apply, in terms of safety, infectivity (attack rate), reproducibility of infectivity, and the dose to be given to volunteers. As for the strains to be selected, it has been suggested (and particularly in the WHO roadmap [9]) to have two representatives of the two most dominant clades. Initially, starting with the wildtype strain is preferred over an agent produced by reverse genetics, although the origin of the wildtype strain needs to be well be described.

The doses suggested by WHO for dose escalation are based on experience in influenza CHIMs. The highest dose, 10^6, is the standard dose used in monkey experiments. This is also given via a very different route, intra-tracheally. If the challenge agent has no effect at 10^6, something must be wrong, no need to go beyond this dose. The use of neutralizing antibodies could be of help in dose selection, however, currently the response to SARS-CoV-2 is not known well enough to rely on this. The protection might be through a mucosal response, including IgM and IgA antibodies as well as T cells; the crosstalk is very complicated.

In terms of dosing, standardization is needed, regarding the strain as well as the virulence, so that dose given to each participant is well characterized. The average titer for the entire lot needs to be known, which eventually gets diluted before use. Back-titration can be done to make sure how much was given rather than a beforehand estimate of what was given. However, it is recommended that the average target dose is verified on each final dose unit before release.

Towards standardization, there is large cross-laboratory variation in standard assays, so if two studies use the same challenge agent, cross-standardization through titration assays should be performed. This is also true for vaccines, so it is not just a CHIM-related problem. While standardization is good, heterogeneity could also add to the results obtained. Hence, having several models, reinforcing or complementing each other, could provide a further insight.

While cell passage is needed to expand the challenge strain, each passage introduces the possibility for genetic change. Therefore, it is essential to ensure that the same challenge agent is used in all participants within any one study, without genetic changes along the way, and with the same infective dose. Quality control and infectivity rates should be stable, including stability over time of the master stock but also of the working stock to be given after final dilution, to confirm stability in case of a delay. However, given the low mutation rate, and the lack of current immunological pressure on the virus, a shift in antigenicity is not expected but should be verified. Hence, using strains from different clades could provide useful insights. If changes in antigenicity are confirmed, this has implications for the vaccine development, and would be important to identify early.

In general, attenuated strains were considered less useful, since clinically relevant circulating strains are needed to arrive at meaningful

conclusions regarding the protective potential of vaccine candidates. Comparative studies using attenuated agents and wildtype strains, have typically shown the superior prognostic value of wildtype strains. Nevertheless, naturally attenuated viruses may be useful in initial dose-finding studies, as further risk mitigation for early studies. Next Generation Sequencing is of great value to screen both wildtype and attenuated strains for adventitious microorganisms.

Could live-attenuated vaccines be used as a challenge agents in CHIM, and also as a vaccine? The polio example was mentioned, where participants are first vaccinated, and then challenge with the same agent after a few weeks, to see if shedding occurs, and this could also be feasible for SARS-CoV-2 as well. However, while this has worked successfully in the past, it may slow the current efforts. Additionally, using a challenge virus homologous to the vaccine will show artificially high efficacy rates. Hence, the challenge should be performed with heterologous strains.

In addition to the specific quality and characterization considerations already mentioned, challenge virus preparations should comply to the standard quality criteria in place for viral agents used in the manufacture of a vaccine medicinal products. General guidelines regarding the required quality parameters, characterization and the quality control strategies for viral vaccines should be considered for the quality control of challenge agents. In addition, clinical trial grade cGMP formulation and storage conditions, as well as stability data for the final preparation should also be documented prior to use. Specific regulators differ in their challenge virus requirements and manufactures were encouraged to contact the responsible agency at an early stage. As a general comment, it was noted that the quality requirements should be at least similar to those of the accompanying vaccine candidate in the same phase, noting that a challenge study would likely be considered as a late phase 2 or phase 3 study. Additionally, since challenge virus will not be administered *via* injection, this may also be a consideration regarding the characterization required of the challenge agent after setting of the relevant formulation and storage conditions.

3.2. Good Manufacturing Practice conditions

The representatives of potential challenge virus manufacturers stressed that their target was to produce GMP, clinical grade material. Additionally, manufacturers and regulators agreed that appropriate quality standards were essential to ensure the safety of CHIM trials, as well as to maintain the trust in the science behind CHIM studies in general. While it was noted that full commercial production GMP compliant validation and conditions would not always be possible, due to small and limited production runs, clinically appropriate standards must be in place, as determined by the competent authority.

While it was noted the not all jurisdictions may have the regulatory authority over challenge materials for CHIM studies, there was a consensus that CHIM studies should not proceed without the above standards in place.

It was also noted that since CHIM studies cannot be undertaken without the manufacture of appropriate clinical grade challenge material, the early development of these key reagents should be the focus of all epidemic/pandemic preparedness planning, so that valuable time is not lost.

4. Panel discussion – regulatory considerations

CHIMs are not only valuable for vaccine development but also for the development of antivirals and monoclonal antibodies or prophylactic treatments. They are of value in proof-of-concept studies, dose-selection and for identifying correlates of protection. Additionally, there are the examples with cholera and malaria vaccines, where approval for some products was based on CHIM data. Discussions regarding the use of CHIMs for SARS-CoV-2 started early, with immediate consideration on the risk for participants. While the current leading vaccine candidates intend to go into large field efficacy phase 3 studies, in such instances, CHIMs could be considered useful to provide ancillary evidence. However, for some vaccines, especially the later candidates, CHIMs might play an essential role if Sponsor's of those vaccines no longer have the realistic opportunity to conduct efficacy studies given potentially low level of circulating virus. This could be seen as defining a potential role for challenge trials in the context of current pandemic in many regions (e.g., Europe, Canada, Japan etc.) where effective disease reducing public health measures have been implemented, but a second wave is still likely. As a result of the scale of the pandemic, we need vaccines to demonstrate safety and efficacy as soon as possible, so that they can be deployed for vaccination of high-risk groups, as well as for the general population. Clinical studies of vaccine candidates have already started according to compressed development plans. CHIMs could be used in combination with phase 3 randomized clinical trials (RCTs) to accelerate product development and possibly reduce the in the amount of evidence required from phase 3 trials.

One aspect regulators are considerably concerned with, is what can be done to mitigate risk for participants. In that respect, rescue therapy is a key factor. There is a tradeoff between the risk for participants and the benefits to society. As noted in the earlier discussions, while attenuated strains would increase safety, the results are less easy to interpret and could lead to studies with no real impact.

It was additionally argued that the value of CHIMs from a regulatory perspective is limited compared to phase 3 trials, as HCT greatly reduced study populations compared to even small conventional phase 3 trials. Furthermore, as no CHIM model is possible for severe disease, HCT might not be able to provide insight into a vaccine's potential to reduce the incidence of severe disease. However, if phase 3 trials are not possible, HCT could become extremely valuable. For efficacy data, the Cholera travelers' vaccine example was mentioned, where the challenges regarding the ability to conduct typical phase 3 efficacy studies was the driver of the CHIM studies. However, this situation is quite different from SARS-CoV-2, where world-wide there are still regions in the world where efficacy studies on SARS-CoV-2 could be conducted. However, those opportunities will only be available for well supported vaccine candidates. Regardless, safety will still have to be adequately investigated pre-approval, to ensure that a positive risk/benefit balance can be defined at time of authorization.

It was noted that regulatory pathways will have to adapt depending on the evolution of the pandemic. As a starting point in the current situation, a conservative standpoint is considered appropriate, but this can be subject to change, and it is difficult to forecast precisely the scenarios that we will be confronted with in the near future.

The question to answer is: when and how does a CHIM add to solving the puzzle. That answer will determine whether CHIMs should be performed. In spite of compelling ethics arguments that support CHIM studies, in the mind of many (but not all) the lack of rescue therapy limits the use of CHIM. While young subjects (e.g., 18–25 years) have been proposed as CHIM participants, even in this population severe COVID-19 have been observed, although at a very much lower rate compared to in the elderly. We will only know how valuable CHIM trials once they are undertaken, and of course the availability of rescue therapy would make thw decision to start much easier for all.

Regardless, all possibilities should to be investigated to speed vaccine clinical development. While the preferred option remains RCT, nevertheless, we should also invest in CHIM, as we don't know how the epidemiology will develop, and whether correlates of protection will be found in RCTs investigating protection. Therefore, CHIMs need to be developed in parallel, so as not to lose time. Given that establishing a conventional CHIM takes approximately a year for logistical reasons, no one wants to look back and realize we did nothing when we had the opportunity to explore this option. We need to have a global view.

The primary endpoint in an HCT will be infection in young adults. However, the target population is elderly with potential comorbidities, with hospitalization and death as endpoints. Some vaccines may not

prevent against infection but may act against the later endpoints disease and death, but this will not be possible to assess directly through CHIMs.

For SARS-CoV-2, a parenteral vaccine is the objective to protect the lungs through a mucosal response, stimulating IgM and IgA antibodies against the receptor-binding domain of the spike protein. While these serological parameters could be assessed in CHIMs, the clinical relevance of such responses in a young population may not be translatable to an elderly population.

An additional concern is the use of CHIM in low- and middle-income countries (LMIC): regulators need to be involved at an early stage. In past, trials have been conducted with only an ethics review board involved, but perhaps a broader communications strategy and consultations should be considered. This can have an impact on acceptance: firstly, to deal directly with a history that have left some people wary that they are being used as Guinea pigs, and secondly because it is feared that positive results in CHIM in a LMIC may lead to a vaccine marketed for use first in HIC. The above and other factors can lead to hesitancy and potentially even resistance to have HCTs run in LMIC. This is counter to the WHO's objectives of global access to the vaccine, with equitable distribution. LMIC regulators are well aware of these issues through the lessons from previous epidemics and pandemics such as Ebola and H1N1 and will benefit through a collaborative approach by all involved, that the LMIC regulators and investigators should direct.

5. Conclusion

The quality of challenge material can be assured by building in safety, using well established quality principles and practices. CHIMs will not be able to provide all answers but are potentially valuable to select between the large number of vaccines and adjuvants available. In specific situations, especially between COVID-19 waves with low circulating virus, CHIMs have the potential to provide more rapid solutions to a global problem. CHIMs could provide data to support or reject vaccine candidates and their indications regarding efficacy, which nevertheless will eventually have to be further supported in a phase 3 and phase 4 clinical trials. These larger trials will be necessary for additional safety and efficacy/effectiveness data, given that HCTs will only enroll limited numbers of participants.

This webinar was undertaken to encourage discussion regarding the use of CHIM for SARS-CoV-2 vaccine development, but not to resolve all issues. As expected, many questions could not be answered definitively, due to a lack of data. However, there was general consensus amongst the panellists that the production of SARS-CoV-2 challenge material must proceed, and that the longer we wait to set up challenge studies, the lower the chance that they will add to regular phase 1–3 trials. And, if phase 3 RCTs provide safety data but cannot provide efficacy data, CHIMs must be ready and available to fill this data gap.

Declaration of competing interest

The authors have no competing interests to declare.

Acknowledgements

The authors are grateful for the support by a grant of Wellcome Trust to organize the webinar; and would like to thank Madinina Cox and Abigail Charlet (International Alliance for Biological Standardization) for logistic management.

References

[1] Baay M, Lina B, Fontanet A, Marchant A, Saville M, Sabot P, et al. SARS-CoV-2: virology, epidemiology, immunology and vaccine development. Biologicals 2020; 66:35–40.

[2] Bekeredjian-Ding I, Van Molle W, Baay M, Neels P. speakers PEI, session c. In: Human challenge trial workshop: Focus on quality requirements for challenge agents, Langen, Germany, October 22, 2019, 66; 2020. p. 53–61. Biologicals.

[3] Ren L, Zhang Y, Li J, Xiao Y, Zhang J, Wang Y, et al. Genetic drift of human coronavirus OC43 spike gene during adaptive evolution. Sci Rep 2015;5:11451.

[4] Lurie N, Saville M, Hatchett R, Halton J. Developing covid-19 vaccines at pandemic speed. N Engl J Med 2020;382:1969–73.

[5] WHO Working Group for Guidance on Human Challenge Studies in COVID-19. Key criteria for the ethical acceptability of COVID-19 human challenge studies. Available from: https://www.who.int/ethics/publications/key-criteria-ethical-acceptability-of-covid-19-human-challenge/en/.

[6] Jamrozik E, Selgelid MJ. COVID-19 human challenge studies: ethical issues. Lancet Infect Dis 2020;20:e198–203.

[7] Shah SK, Miller FG, Darton TC, Duenas D, Emerson C, Lynch HF, et al. Ethics of controlled human infection to address COVID-19. Science (New York, NY) 2020; 368:832–4.

[8] Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, et al. Genomewide association study of severe covid-19 with respiratory failure. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2020283. Epub ahead of publication.

[9] 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 - draft report for public consultation. Available from: https://www.who.int/publications/m/item/feasibility-potential-value-and-limitations-of-establishing-a-closely-monitored-challenge-model-of-experimental-covid-19-infection-and-illness-in-healthy-young-adult-volunteers.