Due to failures in many countries in early prevention, detection of onset, effective quarantine, immediate localization of the pandemic, and/or preventive lockdowns, a global need arose for either effective vaccines that would give societies control over SARS-CoV-2 or other alternatives, such as therapeutic drugs, that would allow humans to coexist safely with the virus. This article focuses on the former issue.

On May 6, 2020, the World Health Organization (WHO) released a document entitled “Key Criteria for the Ethical Acceptability of COVID-19 Human Challenge Studies.” This document was prepared by the WHO Working Group for Guidance on Human Challenge Studies in Covid-19 and proposes key criteria as ethical justification for SARS-CoV-2 human challenge trials. The ethical controversy surrounding human challenge trials derives from the fact that they involve the deliberate infection of human volunteers with potential pathogens, that is, wild-type, attenuated, or genetically modified microbes, not only to increase understanding of the etiology or transmission of infectious diseases but also to facilitate research on effective treatments or prophylaxis and reduce the time required for vaccine development. Human challenge trials have a clear advantage, especially when the infection rate among a population has already gone into declination such that it would be difficult to prove whether a newly developed experimental vaccine is effective. Therefore, the expected value of SARS-CoV-2 human challenge trials to society would indeed be high, as Shah et al. have proposed. At the same time, the known and unknown risks to participants are still substantial and may, in some cases, exceed the expected benefits. It is

**ABSTRACT** In the midst of the ongoing Covid-19 pandemic, researchers across the globe are still working to develop effective vaccines. To expedite this process even further, human challenge trials have been proposed by the World Health Organization (WHO) as an alternative to conventional approaches. In such trials, healthy volunteers are deliberately infected with the pathogen of interest, enabling scientists to study the infection process and facilitate further research on treatments or prophylactics, including vaccines. While human challenge trials would offer a collective benefit to society, minimizing the risks is always difficult. Ethical controversy thus inevitably surrounds these trials. Typically, healthy young adults are recruited to serve as the first candidate subjects for human challenge trials because they are generally considered to represent a low-risk population. Here, we present three reasons for doubt about this healthy-young-adults-first criterion and give justification for also recruiting healthy older adults (or not-young adults), meaning those over 30 years of age, to participate in such trials for SARS-CoV-2.

**KEYWORDS** human subjects research, human research ethics, SARS-CoV-2, Covid-19, human challenge trials, research participants, research subject selection

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crucial that such trials be conducted in accordance with the highest ethical standards and with a reasonably favorable risk-benefit profile.⁵

Among these standards, one common practice recommended by several researchers and guidelines (including the above-referenced WHO document) is the conducting of initial trials with healthy young adults (generally, those aged 18 to 30 years).⁶ However, the healthy-young-adults-first criterion postulated as if it were a gold standard for human challenge trials, particularly with respect to minimizing risk to volunteers, might need to be reconsidered, at least in the case of SARS-CoV-2. Particularly in the case of human challenge trials for vaccines against SARS-CoV-2, we think that what we are calling healthy “older adults” (or “not-young adults”) (conceptually, those over 30 years old) should also be included in the pool of ideal first research candidates. In fact, in some cases, they may even be more suitable than healthy young adults. We raise at least three doubts about the current a priori healthy-young-adults-first criterion proposed by WHO for SARS-CoV-2 human challenge trials and describe reasons for the ethical justification of the recruitment of healthy older adults as the first candidates for these trials.

First, regardless of age, almost all people face a relatively high risk of contracting SARS-CoV-2 in their daily lives, and many will suffer from it if they actually develop the illness after viral infection. Given that all previous attempts to halt the spread of the virus in the early stages were imperfect in many countries, achieving herd immunity—either through vaccination or natural infection with the virus—is the last realistic option in terms of a public health strategy to cohabit peacefully with the virus. And the achievement of proven, truly effective and safe vaccinations takes time, even though the unconfirmed data on practical use in Israel of a developed vaccine is indicating a potential for attaining herd immunity with it.⁷ Irrespective of age, given these high-risk, uncertain circumstances, engaging in a well-controlled and closely monitored human challenge trial may be much safer, at least while the trials are ongoing, than simply waiting for infections to occur at some point in one’s daily life,⁸ even if the viral strain used in the trial is of the dangerous wild-type variety. As generally considered, if and only if young adults are in fact more physically resilient to SARS-CoV-2 and therefore face a lower risk of death relative to their older counterparts, then they are more likely to recover from the disease caused by natural infection. That means that healthy young adults may be the cohort that can wait longer for an established vaccine than older adults can. In addition, if SARS-CoV-2 human challenge trials are conducted with only young adult volunteers, the findings of the trials will inevitably be biased in such a way that they may not directly benefit populations other than young adults because immune responses to SARS-CoV-2 (and, thus, the expected effects of the vaccines) may differ between older and younger adults.⁹ However, if older adult volunteers are also involved in the earliest SARS-CoV-2 human challenge trials that identify effective vaccines, then older populations, who compose the majority of our global society, can be among the first beneficiaries of those vaccines, which will result in better public health consequences. Conducting initial SARS-CoV-2 human challenge trials with older adults would also possibly generate societal benefit more rapidly because the rate of disease and symptom onset after natural infection among older adults is reportedly higher than that among young adults.¹⁰ Accordingly, the healthy-young-adults criterion for these trials can be challenged.

Second, in a typical phase I drug trial for a later-onset common disease, such as hypertension, or type 2 diabetes, that is highly prevalent among the existing population of older people, healthy young adults are usually recruited as volunteers to test the drug’s safety. In addition to the scientific risk-based presumption that their relative youth likely enables them to be healthier and stronger, allowing them to withstand unexpected consequences more readily than older adults,¹¹ one other ethical argument for recruiting healthy young adults first for such trials would be that they will become potential beneficiaries of the candidate drugs in the future when and if they live long enough to be exposed to the disease later in life. In human challenge trials for SARS-CoV-2 vaccine development, a similar but directionally opposite rationale based on the equal sharing of burdens between different generations may be applicable. Specifically, we argue that young people have lived for a much shorter time and now face, just as older adults do, a high likelihood of infection by a potentially deadly virus. Young people face a reality in which they will live much
longer with the risk of infection and potential long-term complications,\textsuperscript{12} such as pulmonary fibrosis, breathlessness, fatigue, chest pain, thromboembolism, ventricular dysfunction, and neurological sequelae,\textsuperscript{13} irrespective of the severity of infection. Meanwhile, healthy older adults have lived longer lives than their younger counterparts and luckily have not previously faced any pandemics of this magnitude. Thus, although there are pros and cons for this argument,\textsuperscript{14} it may also be possible to argue, based on some fair-innings arguments, that older adults as a group actually face lower risks of death in the sense that death for them would represent a loss of fewer years of life than it would for the group of younger adults.\textsuperscript{15} Therefore, the healthy-young-adults-first criterion is again ethically challenged.

Third, even though hospitalization as well as mortality rates for Covid-19 among young adults have been estimated to be lower than those of older adults, it remains unclear whether healthy older adults are really at a higher risk than young adults because many of the reported deaths of older adults have come from nursing homes or other institutionalized settings where most of the residents had some prior health issues.\textsuperscript{16} In addition to the cases reported among older adults, an increasing number of reports have recently emerged regarding the high incidence of various vascular or inflammatory complications experienced by young adults and even children, such as stroke, thromboembolism, or Kawasaki disease-like symptoms, many of which are accompanied by serious and long-lasting symptoms affecting the lungs, kidneys, brain, and heart.\textsuperscript{17} Some young adults are also considered at high risk for experiencing severe symptoms,\textsuperscript{18} in part because members of the younger generation are more likely to be obese than are members of older generations.\textsuperscript{19} Clearly, there is great uncertainty about the risks of SARS-CoV-2 infection across generations once all these risks of various infection-induced damages in addition to the risk of death are taken into account. Thus, the presumption that young adults generally face a lower risk than older adults—and that young adults are therefore more suitable candidates for human challenge trials for SARS-CoV-2 vaccines—may be flawed.

Taken together, the above suggests that the current a priori healthy-young-adults-first criterion for recruitment for these trials may be ethically questionable. Instead, including healthy older adults in addition to young adults in the trials could be justified based on the ethical principle of equal opportunity and that of equal sharing of burdens between generations so long as individuals’ participation is ensured to be voluntary. This seemingly unusual strategy may also result in a more effective public health consequence as a whole and may yield effective vaccines faster in the end.

Given the extraordinary circumstances of the Covid-19 pandemic and the emergent need and ethical justification for human challenge trials to develop effective vaccines as soon as possible, the a priori assumption of the healthy-young-adults-first criterion for such trials must be carefully reevaluated. Not only young but also older populations compose the majority of our global society. If older adults are involved in the earliest SARS-CoV-2 human challenge trials that identify effective vaccines, then older populations can be among the first beneficiaries of those vaccines, which will result in better public health consequences.

Older adults can contribute to developing effective vaccines faster in such an extraordinary situation. Needless to say, this must be voluntary, regardless of age,\textsuperscript{20} and careful consideration is warranted for these reasons to justify ethically the recruitment of healthy older adults first in controversial human challenge trials aimed at addressing the Covid-19 pandemic.

Last but not least, we would like to comment on the world’s first SARS-CoV-2 human challenge trial, expected to start in early spring 2021 in the United Kingdom.\textsuperscript{21} As announced earlier, the volunteers in the trial were recruited from the population of healthy younger people aged 18 to 30. The variant type of the virus used for the trial initially will be one that has been
circulating in the U.K. since March 2020 and is now known to be of low risk to healthy adults (except those over seventy-five). Even in the current Covid-19 circumstances, in which at least some authorized (but not necessarily yet proven) vaccines have become available, we believe that the human challenge trial will help us to accumulate new and important basic knowledge of, for instance, the characteristics of the virus and human immune responses to it. However, this knowledge could be obtained in a different way, other than through human challenge trials. Furthermore, given the present situation, in which so many people have already been infected and so many will sooner or later have been vaccinated with first-generation vaccines, conducting a human challenge trial with a first-generation variant of the virus does not seem very reasonable. If at this moment a human challenge trial were conducted, it should use the most recently evolved variants of unknown but possibly higher risks. Otherwise, the potential to gain useful knowledge for developing effective next-generation vaccines that will satisfactorily justify human challenge trials would be lost. In addition, if conducted, trials with riskier variants should be done fairly, with not only groups of healthy younger people but also groups of healthy older people, as we have discussed.

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