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Human infection studies and the SARS-CoV-2 pandemic

by Jörg Tremmel¹

What could humanity have done better in fighting the SARS-CoV-2 pandemic? From a financial and scientific point of view, it has done many things right, but a crucial ethical question has remained rather unexamined. In this paper, I argue that controlled human infection studies (HIS)² would have been ethically justifiable and the right way forward in developing a vaccine against Covid-19. The phase 2/3 trials of the vaccines from AstraZeneca, Pfizer/Biontech and Moderna took

between 75 and 196 days. Human challenge trials would have taken much less time, about 30 days. In retrospect, these three vaccines could have been launched 45 to 166 days earlier than they actually were. If this had happened, hundreds of thousands of deaths and millions of hospitalisations worldwide could have been avoided due to the cumulative effect. In terms of preparatory measures for the next pandemic, the ethical discussion on HIS is of utmost relevance for the well-being of future generations.

First use of vaccines on humans (phase 1 before approval)

In order to understand the ethical issues surrounding HIS, it is necessary to understand how vaccines are tested on humans in the first place, before the HIS. Once vaccine developers have tested a certain agent against an infectious disease in animals (“preclinical studies”) and these creatures have been successfully immunised, the next step is the first application in humans. The immune system of humans is so fundamentally different from that of even the animals most similar to us, that the approval of an investigational vaccine solely on the basis of animal experiments is not an option. Depending on the number of test persons and the exact question, a distinction is usually made between three phases (and occasionally a phase 4 after approval) in human application. For human volunteers, phase 1 (“first in human”), is the riskiest. The author of this text participated in the phase 1 trial of CureVac³ as a subject and received 8µg of the investigational vaccine (CVnCoV) twice.

How would one have proceeded in a “human infection study”? Regulatory authorities need data on the efficacy of vaccine candidates beyond the results of the phase 1 trial for their decisions. The sequence of studies until submission for licensure is described in chart 1.

How approved vaccines against Covid-19 were actually tested “in the field”?

Time is the decisive factor in protecting future generations from new pandemics.⁴ As HIS studies can replace phase 2/3 studies (but not phase 1 studies), it is important to know exactly how long the phase 2/3 studies lasted.⁵ Chart 2 shows the relevant data for the first vaccines approved in the EU and the USA, i.e. those from Pfizer/Biontech, Moderna and AstraZeneca,⁶ as well as for the CureVac vaccine CVnCoV.⁷

Chart 1: Process to SARS-CoV2 vaccine licensure, including a human infection study

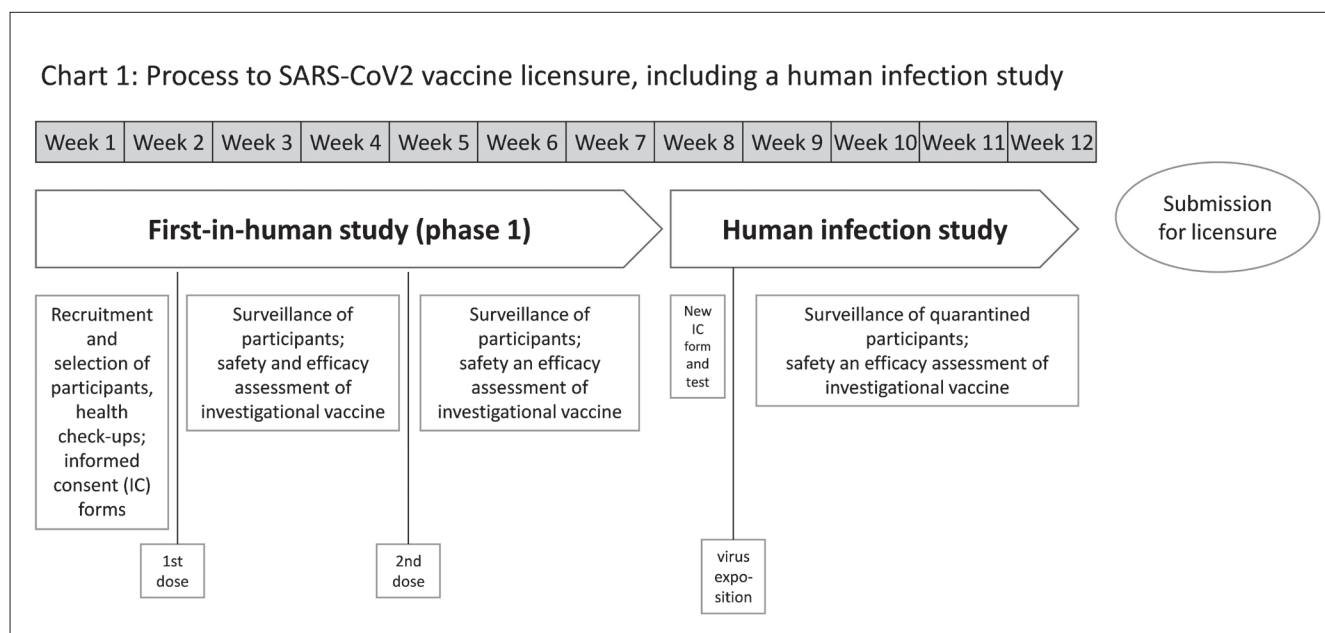


Chart 2:

	Duration of the phase 2/3 study	Participants	Infected persons in the active agent group	Infected persons in the placebo group	Effectiveness of the vaccine
BNT162b2 (Pfizer/ BioNTech)	75 days 27.07.2020 - 09.10.2020	43.448	8	162	95%
mRNA-1273 (Moderna)	112 days 27.07.2020 - 15.11.2020	30.420	11	185	94,1%
ChAdOx (AstraZeneca)	196 days 23.04.2020 - 4.11.2020	23.848	The values of these columns are not comparable, as the phase 3 study was divided into two sub-studies, and the summation of the values was strongly criticised within the scientific community.		
CVnCOV⁸ (CureVac)	123 days 11.12.2020 - 12.04.2021	39.680	83	145	48,2%

The phase 3 trials of the first vaccines approved in the EU and the USA took between 75 and 196 days, depending on the vaccine. Human infection studies would have taken significantly less time, about 30 days. In retrospect, therefore, the vaccines that were gradually approved could have been on the market 45 to 166 days earlier than they actually were. Indeed, a large number of deaths and hospitalisations could have been avoided if HIS had been used instead of the usual phase 2/3 trials.

Without HIS, the following adversities occur. The stronger the protective measures (“lockdown”), the more months are lost. How many infected people there must be before the regulatory authorities are satisfied is an opaque process. This is where vaccine manufacturers and regulatory authorities have to come to an agreement. Ultimately, these are negotiation processes that are hidden from the public. Different actors – the government, the regulatory authorities, the public – have different ideas, which can lead to tensions. An example from Turkey: “The Turkish researchers, speaking alongside Health Minister Fahrettin Koca, said 26 of the 29 people who were infected during the trial were given placebos, adding the trial would continue until 40 people become infected. (...)” Health Minister Koca said Ankara would now – this was on 24.12.2020 – use this data to approve the vaccine. He added that “researchers initially planned to announce the results after 40 people were infected, but that the findings showed the volunteers had minimal adverse effects after the shot and that it was therefore deemed safe.”⁹ Incidentally, the vaccine in question was China’s Sinovac vaccine, and the vaccine effectiveness of 91.25% calculated on the basis of the small number of cases, which the Turkish health minister communicated to the public, is doubtful. However, this is also true for the decimal places in the vaccine efficacy calculated by e.g. PfizerBiontech or Moderna from the low infection cases of their respective studies. Waiting to see when 10, 20, 30, 40, 60, 80 or 100 vaccinated people will “accidentally” be infected is gruelling when the whole world is waiting for a vaccine. And the small numbers lead to unsatisfying data about vaccine effectiveness.

Existential risks for future generations – ethical requirements for HIS in general

In addition to anthropogenic climate change, a possible nuclear war and other factors, epidemics are among the existential risks for future generations. The potential of HIS is undisputed and was once again highlighted by the WHO in 2020 during the first wave of the Corona pandemic: “Well designed human challenge studies provide one of the most efficient and scientifically powerful means for testing vaccines, especially because animal models are not adequately generalisable to humans. Challenge studies could thus be associated with substantial public health benefit in so far as they (a) accelerate vaccine development, (b) increase the likelihood that the most effective (candidate) vaccines will ultimately become available, (c) validate tests of immunity, and (d) improve knowledge regarding SARS-CoV-2 infection and transmission.”¹⁰

Can the worst effects of pandemics be avoided in *general*, *i.e. also in the future*, if humanity relies on HIS? That depends on many virological-medical factors. From an ethical point of view, one cannot come to a simple yes or no conclusion in respect to HIS. The following factors and framework conditions play a role in determining the answer:

Benefit of a vaccine – disadvantages for society as a whole without HIS

HIS have helped in the early research with smallpox, yellow fever and malaria that eventually changed the course of global public health. And HIS have recently helped, for example, to accelerate the development of vaccines against typhoid and cholera.¹¹ Whether vaccines help in the long term depends also on the ability of a virus to generate immune escape variants. The ability to mutate varies from the genetically stable smallpox virus at one end of the scale to the very rapidly mutating influenza viruses at the other. SARS-CoV-2 is somewhat in the middle. This means vaccination is a useful but not a perfect remedy. This is the case for most infectious diseases. All experts agree: If mankind had failed to develop vaccines against SARS-CoV-2, the death toll would have been much higher. Georg Schmidt, chairman of the Working Group of Medical Ethics Committees in Germany, is of the opinion that one can consider conducting a HIS only if the risk is manageable and a social catastrophe is imminent. With regard to Covid-19, according to Schmidt, this is not the case in the current situation.¹² Not a catastrophe? Peer-reviewed global estimates of excess deaths indicate 18.2 million people may have died because of the COVID-19 pandemic by December 31, 2021.¹³ The global Corona pandemic was very much a catastrophe, especially for the most vulnerable members of society. Next to the millions of deaths and long-haul Covid cases we should not forget all the liberty rights restrictions due to lockdown measures, and the lost livelihoods due to economic depression. What is correct is that the sheer size of the catastrophe is an important factor in the ethical assessment of HIS. The more a pathogen poses an existential risk to humanity, the more HIS are justified.

Benefits of HIS for vaccine research

The best possible design of vaccine trials, including how many sequential trials there should be, varies from pandemic to pandemic. However, the tendency is that HIS can generate extremely important data for vaccine development. In the case of the SARS-CoV-2 pandemic, the objection to HIS was that the data obtained in young, healthy volunteers could not be transferred to the vulnerable group of people over 70. The WHO disagrees: “Prioritizing the safety of participants is standard in modern challenge studies and acceptable in so far as studies with low-risk participants nevertheless produce useful results”¹⁴

Health risks for the test persons

The lower the health risks associated with HIS, the more likely they are to be ethically permissible. A specific assessment is always required. In the case of SARS-CoV-2, there were still many uncertainties in the initial phase regarding the pathogenicity or lethality of the virus. There were also no effective drugs or therapies against SARS-CoV-2 in 2020-2021. Unlike, for example, malaria, influenza, typhoid and cholera – diseases for which controlled infection studies have been and are being conducted. The risks to the subjects are reduced when there is excellent diagnostics so that action can be taken within a sufficiently long incubation period before the disease becomes life-threatening. This was not the case with SARS-CoV-2. And as there was no effective therapy, the health risks for HIS test persons in early 2020 were high.

Ethical Assessment

All in all, human autonomy should be the deciding argument. In many contexts, our society allows adults to help others at the risk of their own lives.

Examples of ethical analogies to participation in HIS:

– members of volunteer fire brigades are allowed to run into burning buildings to save lives at the risk of their lives and without financial compensation (unlike professional firefighters).

– doctors or nurses are allowed to travel to war zones at their own risk to alleviate suffering.

– In particular, it is incomprehensible why our society legally allows phase 1 trials in vaccine development, but not subsequent human infection trials. As made clear in the first part of this text, the phase 1 trial subjects also took a risk.

As long as someone can assess the risk to themselves, they should be allowed to act altruistically, even at the risk of their health or even their life.

By the way, it is young people who have joined forces to enable controlled infection studies in which they themselves want to participate as test persons.¹⁵

Notes

1 This is an abridged version of an open letter to the German Ethics Council, available at: generationengerechtigkeit.info

2 Synonyms are Human Challenge Studies (HCS) or Human Challenge Trials (HCT).

3 Kreamsner / Mann / Kroindl et al. 2021a.

4 FRFG 2021

5 This refers to the large trial study with thousands of participants. In practice, this is not always referred to as Phase 3, but also as Phase 2/3, Phase 2a/3 or Phase 2b/3, depending on the circumstances.

6 Johnson&Johnson is not included here because only one dose was administered here. This automatically reduces the time for the clinical trials. As it turned out, however, the immune protection also suffered.

7 Baden / El Sahly / Essink et al 2021; Polack / Thomas / Kitchin et al 2020; Voysey / Clemens / Madhi et al 2021; Kreamsner / Guerrero / Arana-Arri et al 2021b.

8 It is obvious that CureVac came along later than the competing companies. The Paul Ehrlich Institute had already approved the first "first in human" study of a vaccine against Covid-19 in Germany on 22 April 2020, namely for four mRNA-based vaccine candidates from the company BioNTech. CureVac ultimately had to refrain from further seeking market approval from the regulatory authorities due to the lower efficacy of its vaccine compared to the vaccines approved until the end of 2020.

9 <https://www.reuters.com/article/health-coronavirus-turkey-china-int/turkey-says-chinas-sinovac-covid-vaccine-9125-effective-in-late-trials-idUSKBN28Y1R3>. Viewed 24 December 2020.

10 WHO 2020: 2.

11 WHO 2020: 2

12 Reich 2021.

13 Wang 2022.

14 WHO 2020, 14.

15 See: www.1daysooner.org

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