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Narrative Review

COVID-19 vaccine research and development: ethical issues

T. Wibawa[1,2]

1 *Department of Microbiology, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia*
2 *Medical and Health Research Ethics Committee, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada / Dr. Sardjito General Hospital, Yogyakarta, Indonesia*

Abstract The achievements of vaccine research and development bring a hope to our societies that we may cope with the COVID-19 pandemic. There are two aspects that should be maintained in balance: the immediate necessity for speed of vaccine research and the inherent need for protection of research subjects, which is the foremost concern of research ethics. This narrative review highlights ethical issues in COVID-19 vaccine research and development that every stakeholder needs to be aware of and to consider.

keywords COVID-19, vaccine research, ethics

Sustainable Development Goals (SDGs): SDG 3 (good health and well-being)

Introduction

COVID-19 is a deadly disease which continues to affect many countries in the world. The incidence is higher in the Americas (14 117 714 cases and 486 843 deaths) and Europe (4 515 514 cases and 222 624 deaths) than in South East Asia (4 786 594 cases and 84 541 deaths), Africa (1 088 093 cases and 23 101 deaths) and the Western Pacific (520 012 cases and 11 306 deaths) [1].

Vaccines are the most important public health measure to protect people from COVID-19 worldwide, since SARS-CoV-2 is highly contagious and infects populations widely and globally [2]. Traditionally, vaccine development takes years, even decades: from about 40 years for polio to 5 years for Ebola,most vaccines took 15 years on average [3,4]. The trial process for vaccines consists of several steps which need to be conducted systematically and in a measurable stride. The length of this process is correlated with the nature of the vaccine itself, which is to protect healthy people from being infected by pathogens. Adverse events and deleterious effects will not be tolerated, vaccines are not the same as drugs that are consumed by the sick. The risk–benefit analysis for prescription drugs and vaccine administration is different.

The invention of a successful and widely available COVID-19 vaccine will be a great leap forward for humankind, but there are several challenges to overcome: (1) a lack of understanding of the pathogenesis and the predictive role of vaccines in the clinical pathway of persons being infected by SARS-CoV-2 [5–7], (2) a huge disagreement among experts about how to determine the most immunogenic epitopes and antigens of SARS-CoV-2 [8,9], (3) the finding that antibody-dependent enhancement (ADE) may contribute to the exaggeration of SARS-CoV-2 disease [10,11], (4) the lack of established animal models for COVID-19 vaccine challenge testing, which raises the speculation of using controlled human infection (CHI) as a potential approach [3], and finally, (5) speculation that the duration of protection by immune response in natural infection is not long enough [12].

The race for COVID-19 vaccine invention and development against the spread and catastrophic effects of the disease is real. WHO released a draft list of COVID-19 candidate vaccines on 3 September 2020. At least 34 vaccine candidates are in clinical evaluation to date [13]. Several new technologies are used as COVID-19 vaccine development platforms. Conventional techniques for the development of vaccines such as inactivated, inactivated with adjuvant and live attenuated are still being used. However, reversed vaccinology approaches are also being emplyed, such as a recombinant subunit vaccine, and a more advanced approach using vector delivery systems, along with RNA- and DNA-based vaccines (Table 1) [4,9,13].

The attempts to accelerate vaccine development are associated with efforts to streamline the process. Unfortunately, streamlining may have consequences for the traditional ethics of vaccine research and development, especially the long-held principles of beneficence and non-maleficence. This short narrative review summarises the ethical issues

Table 1 Candidate COVID-19 Vaccines in Clinical Trial Phases*

No	Vaccine Platform	Type of Candidate Vaccine	Developer	Current stage of clinical evaluation
1	Non-Replicating Viral Vector	ChAdOx1-S	University of Oxford/AstraZeneca	Phase 1/2; Phase 2; Phase 3
2	Non-Replicating Viral Vector	Adenovirus Type 5 Vector	CanSino Biological Inc./Beijing Institute of Biotechnology	Phase 1; Phase 2; Phase 3
3	Non-Replicating Viral Vector	Adeno-based (rAd26-S + rAd5-S)	Gamaleya Research Institute	Phase 1; Phase 3
4	Inactivated	Inactivated	Sinovac	Phase 1/2; Phase 3
5	Inactivated	Inactivated	Wuhan Institute of Biological Products/Sinopharm	Phase 1/2; Phase 3
6	Inactivated	Inactivated	Beijing Institute of Biological Products/Sinopharm	Phase 1/2; Phase 3
7	RNA	LNP-encapsulated mRNA	Moderna/NIAIDRNA	Phase 1; Phase 2; Phase 3
8	RNA	3 LNP-mRNAs	BioNTech/Fosun Pharma/Pfizer	Phase 1/2; Phase 3
9	Protein Subunit	Full length recombinant SARS-CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	Novavax	Phase 1/2; Phase 2b
10	Protein Subunit	Adjuvanted recombinant protein (RBD-Dimer)	Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences	Phase 1; Phase 2
11	RNA	mRNA	Curevac	Phase 1; Phase 2
12	Inactivated	Inactivated	Institute of Medical Biology, Chinese Academy of Medical Sciences	Phase 1; Phase1/2
13	Inactivated	Inactivated	Research Institute for Biological Safety Problems, Rep of Kazakhstan	Phase1/2
14	DNA	DNA plasmid vaccine with electroporation	Inovio Pharmaceuticals/ International Vaccine Institute	Phase1/2
15	DNA	DNA plasmid vaccine + Adjuvant	Osaka University/ AnGes/ Takara Bio	Phase1/2
16	DNA	DNA plasmid vaccine	Cadila Healthcare Limited	Phase1/2
17	DNA	DNA Vaccine (GX-19)	Genexine Consortium	Phase1/2
18	Inactivated	Whole-Virion Inactivated	Bharat Biotech	Phase1/2
19	Non-Replicating Viral Vector	Ad26COVS1	Janssen Pharmaceutical Companies	Phase1/2
20	Protein Subunit	RBD-based	Kentucky Bioprocessing, Inc	Phase1/2
21	Protein Subunit	S protein (baculovirus production)	Sanofi Pasteur/GSK	Phase1/2
22	RNA	mRNA	Arcturus/Duke-NUS	Phase1/2
23	Non-Replicating Viral Vector	Replication defective Simian Adenovirus (GRAd) encoding S	ReiThera/LEUKOCARE/Univercells	Phase 1
24	Protein Subunit	Native like Trimeric subunit Spike Protein vaccine	Clover Biopharmaceuticals Inc./GSK/Dynavax	Phase 1
25	Protein Subunit	Recombinant spike protein with Advax™ adjuvant	Vaxine Pty Ltd/Medytox	Phase 1
26	Protein Subunit	Molecular clamp stabilised Spike protein with MF59 adjuvant	University of Queensland/CSL/Seqirus	Phase 1
27	Protein Subunit	S-2P protein + CpG 1018	Medigen Vaccine Biologics Corporation/NIAID/Dynavax	Phase 1
28	Protein Subunit	RBD + Adjuvant	Instituto Finlay de Vacunas, Cuba	Phase 1
29	Protein Subunit	Peptide	FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo	Phase 1
30	Protein Subunit	RBD (baculovirus production expressed in Sf9 cells)	West China Hospital, Sichuan University	Phase 1

Table 1 (*Continued*)

No	Vaccine Platform	Type of Candidate Vaccine	Developer	Current stage of clinical evaluation
31	Replicating Viral Vector	Measles-vector based	Institute Pasteur/Themis/Univ. of Pittsburg CVR/Merck Sharp & Dohme	Phase 1
32	RNA	LNP-nCoVsaRNA	Imperial College London	Phase 1
33	RNA	mRNA	People's Liberation Army (PLA) Academy of Military Sciences/Walvax Biotech.	Phase 1
34	VLP	Plant-derived VLP adjuvanted with GSK or Dynavax adjs.	Medicago Inc.	Phase 1

*Modified from (13).

that may emerge from the current directions in COVID-19 vaccine research and development during the pandemic.

Safety

Vaccine candidates must fulfil several requirements: safety, efficacy and quality. Because of the current escalation of the global COVID-19 pandemic, some aspects may change. The speed of vaccine development may push public health ministers, heads of states and the pharmaceutical industry to change their strategy for bulk budget investment for vaccine research. They must decide to prepare mass production events based on the limited data of promising vaccine candidates [14]. The need to protect billions of earth's inhabitants pushes governments and societies of the world to a 'great expectation' for the new vaccine. The overriding expectation, although with diverse interests, may influence the objective judgement typically required of candidate vaccine safety. Protecting human lives should be the priority.

mRNA- [15] and DNA-based vaccine technologies [9,16] are being implemented in humans, especially as vaccine candidates. Several concerns about mRNA vaccine safety have been identified besides its promising potential advantages. The most important risks include the possibility that mRNA vaccines may generate strong type I interferon responses that could lead to inflammation and autoimmune conditions [17]. The safety concerns of DNA-based vaccines involve the possibility that the targeting of DNA into the chromosomal DNA of the acceptor will trigger mutagenic effects in the functional gene located in the insertion loci [18]. At present, there are no mRNA- and DNA-based vaccines against any disease authorised to be marketed.

The strategy of DNA vaccines is similar to gene therapy in that a delivery system, such as plasmid, delivers targeted DNA into cells, where it is translated into proteins that induce the acceptors' immune response to generate targeted T-cell and antibody responses [19]. We have experience in using DNA for several gene therapies mostly related to inherited diseases or familial predispositions. Mainstream gene therapy scientists have stated that gene therapy is only suitable for terminally ill patients because the risks are very high [20]. Vaccine administration is completely different from interventions with gene therapy since the vaccine is for healthy human subjects, and the risk–benefit consideration would be completely different too. Both terminally ill and healthy persons have the same risk for the introduction of foreign DNA into their body, but terminally ill persons may benefit through having a chance to recover from

their deadly disease, whereas healthy individuals may not have any benefit because they have never encountered the particular pathogen.

When we perform the risk assessment of new technology, it is based on a theoretical framework without direct evidence concerning to what extent the probability of the risk may occur. Theoretically, DNA vaccine may be able to induce autoimmune diseases and can be inserted into any part of the chromosomes [21]. Scientists know how the mechanism works and are able to predict the risk if it might happen. But nobody knows for certain how great the probability is of producing mutagenic and deleterious effects in one part of a gene sequence when inserted into another. For example, when a test subject named Jessie Gelsinger was injected with adeno-associated viruses (AAVs), nobody expected the deadly risk that ultimately occurred in this research subject [22]. Accordingly, the risk–benefit assessment in the use of new technology should be done carefully. It is true that sometimes we have to deal with a risk possibility that is not immediately present but theoretically possible, and vice versa. Mitigation to the deleterious effect could be started prior to the clinical trial. However, there is always the possible existence of risks that have not been identified yet and will only show in the later phases of clinical trials.

In the current pandemic, all societies expect a breakthrough in medical and health technology. In a situation where understanding of the new disease is poor and no satisfactory medical technology is available for prevention and treatment yet, it is natural to think that 'doing something is better than nothing'. This is going to make safety judgement among stakeholders more prone to deterioration.

Controlled human infection (CHI)

One of the crucial steps of vaccine development is the challenge test, which is used to measure the potential protection of the candidate. The challenge test is usually part of the pre-clinical study in an animal model. However, in the case of COVID-19 and some other diseases, an animal model is not available, although there are candidates that need to be verified [3,23–25]. It seems the pathogen does not produce a similar clinical course in common animal models, which excludes safety and efficacy data from animal models alone. There was a proposal of human challenge testing to replace the pre-clinical challenge test in animal models, with the use of controlled human infection (CHI). It will solve the problem of the animal models' unreliability and gain time for the developers especially in phase III [3,26].

To some extent, it is possible to perform these challenge tests with human volunteers. It sounds like an unsafe experimentation, but the choices are extremely limited. The next question is how can we do this experiment with the current ethical review process? The WHO has issued a guideline for CHI [27]. The guideline is broad and needs local ethics committee approval for its implementation. Considerations of the pros and cons of CHI are widely discussed in COVID-19 vaccine development. Previously, CHI was used to develop vaccines against malaria [28], typhoid [29] and cholera [30], which are diseases with established treatment [31]. Subjects who suffered from deleterious effects after experimentation could be rescued by the established treatment. Application of CHI in COVID-19 is a very different story because there is no standard treatment for this new and highly contagious disease. Nevertheless, there have been thousands of volunteers from 162 countries who declared their willingness to be participants in this CHI [32]. The need for a vaccine is prevalent in people's minds and equally necessary from the public health point of view. Without any precedents, it is going to be difficult to judge the risks benefits in this matter [33].

Controlled human infection could be done in a situation where there is an attenuated virus strain available, for example, using an artificial mutant virus. This approach is to prevent fatal outcomes in trial subjects. But the challenge test results from attenuated virus may not be generalisable – the attenuated strain may not be similar enough to the naturally circulating virus. In addition, producing the attenuated virus may require another step that will take almost as much time to perform as the regular phase III in typical controlled clinical trials. This additional step in an already complicated process will render futile the main purpose to gain more time to develop an effective vaccine [34].

Location and population

Development sites of COVID-19 vaccines are involving research subjects from many countries, for example USA, Russia, Argentina, Brazil, Germany, India, Saudi Arabia, Pakistan and others [35]. The need of multi-centred research is obvious in the vaccine development. The safety, tolerability, and efficacy of the vaccines should be obtained from different geographic areas, ethnicities, prevalence and varieties of the virus circulating in the areas [36]. The attempt to fulfil this requirement may result in the involvement of countries with limited resources and whose underdeveloped infrastructure would make the people involved become even more

vulnerable as research subjects from the ethical and humane point of view. The possible exploitation of vulnerable people from less developed countries should be reviewed thoroughly. The vaccine trial should give them equitable advantages in trade, such as capacity building, transfer of technology and access to the vaccine during the current pandemic of COVID-19.

Another concern is the availability of an adequate health facility and system to ensure that trial subjects and their families and/or communities have access to treatment and proper care in case of serious adverse events related to the trial outcomes. This must be assessed before any clinical trials begin. Providing the most comprehensive health services to the trial population will be an added value for population involvement in the trial. The best practice of vaccine clinical trials should have direct benefits for the community, such as improvement and availability of basic health facilities [37]

Vaccine acceptors are sometimes segmented into target groups, which is related to the host distribution of the target disease, *for example* by gender, age and specific population in the endemic area. A vaccine clinical trial is usually started in adult subjects and continued to more vulnerable subjects such as infants, young children, the elderly and women. Clinical vaccine trials will recruit vulnerable subjects. Protection measures to safeguard the vulnerable and marginalised populations should be carefully scrutinised during review. Ethical considerations must be adjusted to the individual situation to protect these vulnerable subjects from exploitation and later abandonment [38].

However, in an emergency pandemic situation, the definition of vulnerability needs to be openly discussed, and emergency calls for exceptions. The exclusion of vulnerable groups may diminish trial validity because of selection bias, so they should not be excluded without reasonable scientific and ethical justification [39].

Post-trial access

After clinical vaccine trials, the subjects should have access to the developed vaccine. This is part of their direct advantage for their involvement in the research. While it is mentioned in the international ethical guidelines, not all researchers know and are aware of this important obligation [40]. The current COVID-19 vaccine development involves multi-country and intercontinental research recruiting subjects from different countries and regions. The post-trial access to COVID-19 vaccines should be expanded beyond the community where the trial is performed to include the country and region.

Post-trial access is a matter which must be addressed from the very beginning of research design. Community engagement should be considered prior to the trial and involve all stakeholders: sponsors, industries, developers, investigators, subjects of the trial, communities and the government where the trial is performed.

In summary, the current COVID-19 vaccine research and development involves people from many countries, which raises ethical issues that must be addressed by all stakeholders. Even in the emergency of a pandemic, the urgency of providing an effective COVID-19 vaccine for humankind must be balanced with the exigency of research ethics that must be maintained. In any event, the safety and well-being of research subjects must be protected, especially that of vulnerable subjects.

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Corresponding Author Tri Wibawa, Department of Microbiology, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Jl. Farmaco, Sekip Utara, Yogyakarta 55281, Indonesia. Phone +62274580297; Fax +62274581876; E-mail: twibawa@ugm.ac.id