Tidsskriftet
DEN NORSKE LEGEFORENING

Status of COVID-19 vaccine development

PERSPECTIVES

ARNE MICHAEL TAXT

E-mail: arntax@ous-hf.no
Arne Michael Taxt is a specialist in paediatrics, assistant doctor and researcher at the Department of Microbiology, Oslo University Hospital. He has a PhD in vaccine development.
The author has completed the ICMJE form and declares no conflicts of interest.

GUNNVEIG GRØDELAND

Gunnveig Grødeland is head of the Influenza and Adaptive Immunity research group at the Department of Immunology and Transfusion Medicine, University of Oslo and Oslo University Hospital.
The author has completed the ICMJE form and declares no conflicts of interest.

ANDREAS LIND

Andreas Lind is a specialist in internal medicine, infectious diseases and medical microbiology. He is a senior consultant and head of unit at the Department of Microbiology, is in charge of viral diagnostics – including SARS-CoV-2 analyses – at Oslo University Hospital, Ullevål, and has a PhD in immune responses to therapeutic HIV vaccination.
The author has completed the ICMJE form and declares no conflicts of interest.

FREDRIK MÜLLER

Fredrik Müller Dr.med., is a specialist in medical microbiology, professor at the University of Oslo, and head of the Department of Microbiology, Oslo University Hospital.
The author has completed the ICMJE form and declares no conflicts of interest.

The pandemic caused by SARS-CoV-2 has created a global humanitarian and economic crisis for which there is currently no solution in sight. Much hope has therefore been pinned on a vaccine that can protect against the disease COVID-19. As of August 2020, the World Health Organization has registered 173 vaccine candidates as being in development. Six candidates have entered phase 3 trials, and the first results from these are expected in the autumn.

The world is in the midst of a pandemic caused by *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2), which originated in Wuhan in the Hubei Province of China in the final months of 2019 (1, 2). SARS-CoV-2 causes the disease COVID-19 (coronavirus disease 2019) and can give rise to a highly variable clinical picture, ranging from a mild upper respiratory tract infection to severe respiratory failure resulting in death. The precise case fatality rate of COVID-19 is very difficult to estimate, primarily because many people are likely to contract and recover from the infection without being tested. Other factors including age, treatment availability, underlying diseases, and overweight also affect the case fatality rate, but the World Health Organization (WHO) suggests a general case fatality rate for SARS-CoV-2 of around 0.5–1.0 %.

Different countries have chosen to deal with the pandemic in very different ways. In Norway, large parts of society were locked down on March 12th this year, whereas Sweden's strategy through the spring of 2020 was to protect vulnerable groups of the population, while otherwise allowing the pandemic to run its course in order to achieve herd immunity relatively quickly. Unfortunately, population studies from the Stockholm area (3) and Spain (4) show disappointingly low SARS-CoV-2 seroprevalence even in areas with high infection transmission rates and high mortality. It is possible that studies which include T cell immunity may improve this picture somewhat, as cellular immune responses have been demonstrated in infected individuals where seroconversion was not observed (5). However, a strategy based on achieving herd immunity through SARS-CoV-2 infection seems like a painful path to follow. We do not yet know the full extent of the effects of the Norwegian strategy with its major

lockdown of society, but it is obvious that this strategy too has had consequences for life and health and has also been economically extremely costly. Against this backdrop of humanitarian and economic crisis, great expectations rest on the development of a vaccine that can protect against COVID-19.

Biology and antigens

SARS-CoV-2 is an enveloped positive-stranded RNA virus in the family *Coronaviridae*. There are more than 35 known coronaviruses (6) that infect various mammals, including bats, pigs, cattle, chickens, dogs and cats (7). Seven of these viruses can currently infect humans. The virus family is further divided into four genera: alpha, beta, gamma and delta coronavirus. SARS-CoV-2 is a beta-coronavirus, as are two other feared human-pathogenic coronaviruses with epidemic potential, namely SARS-CoV-1 and MERS-CoV (Middle-East respiratory syndrome coronavirus).

In 2003, SARS-CoV-1 caused a major global outbreak that spread rapidly from the Guangdong province in China to at least 26 different countries, resulting in 8 096 infections and 774 deaths (8). MERS-CoV has to date mainly caused outbreaks limited to the Arabian Peninsula, with more than 2 000 confirmed cases and over 700 deaths (9). Additionally, four coronaviruses circulate in the population and give rise to colds and respiratory tract infections of varying severities, but rarely cause serious illness. These viruses, two of which are beta-coronaviruses (HCoV-HKU1 and HCoV-OC43) and two of which are alpha-coronaviruses (HCoV-229E and HCoV-NL63), are thought to cause 15–30 % of all respiratory tract infections (7).

The genome of SARS-CoV-2 consists of approximately 30 000 nucleotides and encodes four structural proteins referred to as spike protein (S), membrane protein (M), nucleocapsid (N) and envelope protein (E) (10) (Figure 1). The genome also encodes 23 non-structural proteins, including an RNA polymerase (10, 11). S proteins characterise all coronaviruses: they cover the surface of the virus and resemble a corona on electron microscopy, hence the family name *Coronaviridae*. The S protein of SARS-CoV-2 contains a domain that interacts with the human receptor angiotensin-converting enzyme 2 (ACE2), which facilitates uptake of the virus into the body's cells (12). SARS-CoV-1 and the common cold virus HcoV-NL63 also use this uptake mechanism, but the other coronaviruses do not (2, 13). ACE2 is expressed on epithelial and endothelial cells, including lung tissue, intestines, kidneys and heart (14).

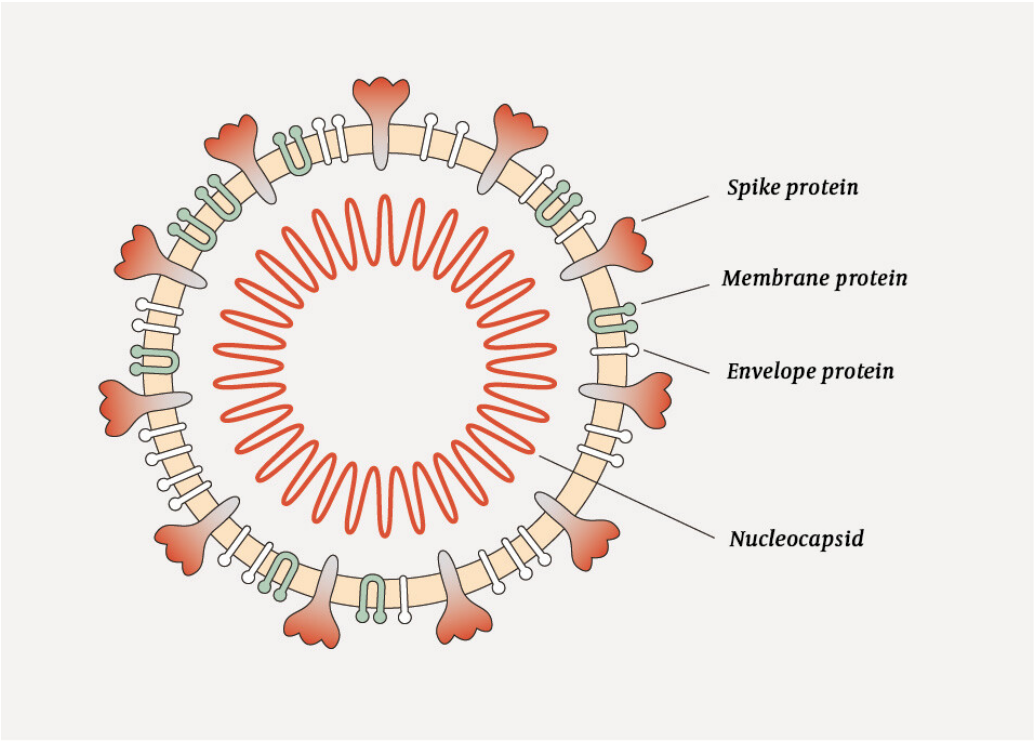

Figure 1 Schematic illustration of SARS-CoV-2 showing the four structural proteins: spike protein (S), membrane protein (M), envelope protein (E) and nucleocapsid (N). The S, M and E proteins are anchored in the lipid bilayer that makes up the viral membrane. The N protein is associated with viral RNA on the inside of the membrane. Modified from Desiree Ho, the Innovative Genomics Institute. CC BY-SA (https://creativecommons.org/licenses/by-sa/4.0).

The S protein is the primary antigenic target in the development of vaccines against SARS-CoV-2 (Figure 2), the aim being to generate an immune response that prevents the virus from interacting with ACE2. Specifically, the vaccine molecule should mimic epitopes in the area of the S protein that is in direct contact with the human receptor, the receptor binding domain (RBD). It is now well established that an immune response to the S protein is generated as a result of infection with SARS-CoV-2, and in vitro studies with convalescent sera have shown that anti-S antibodies are able to neutralise the virus in cell culture and prevent its interaction with ACE2.

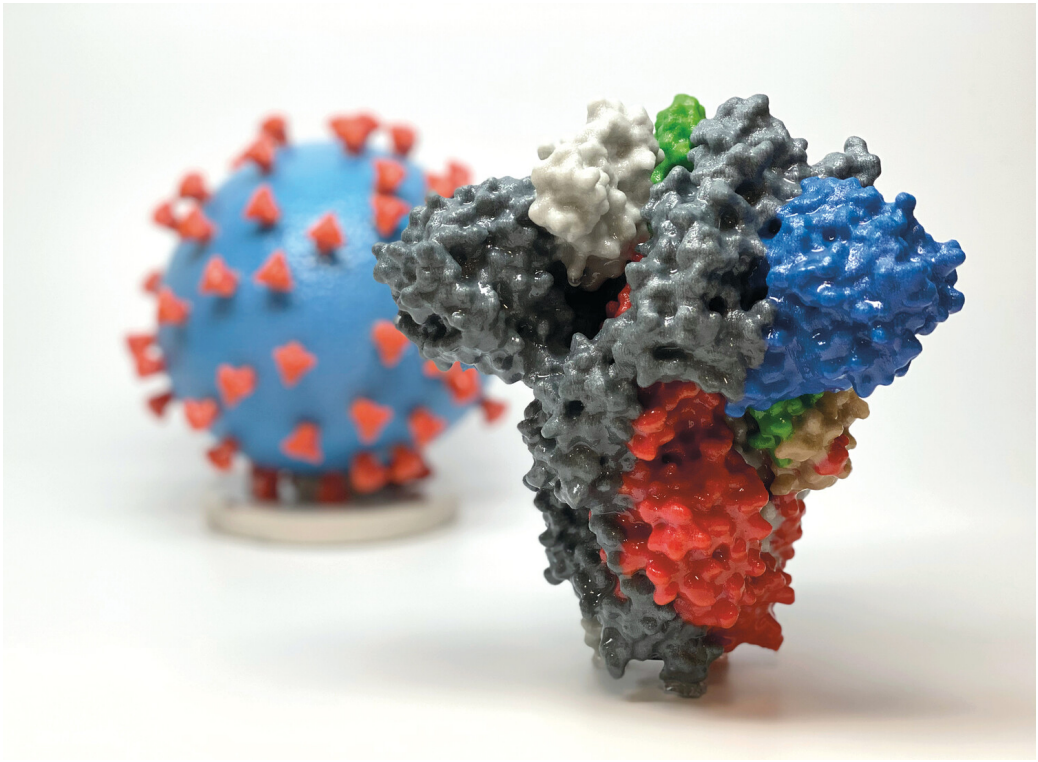

Figure 2 3D printed structural model of the spike protein (S) of SARS-CoV-2 viewed from the side. The S protein is the primary antigen in vaccines against COVID-19. It is a surface-exposed glycoprotein composed of three identical protomers and undergoes a structural change when it binds to the human receptor angiotensin-converting enzyme 2. In the figure, one protomer is given colour, with green indicating the receptor-binding domain. A model of a SARS-CoV-2 virus particle can be seen in the background. From the National Institute of Allergy and Infectious Diseases (NIAID) / CC BY (https://creativecommons.org/licenses/by/2.0).

The three other structural proteins (M, N and E) are not currently considered as important in the context of a vaccine, and the relevance of antibodies against these antigens is unclear. The N protein is not a surface protein, but is associated with viral RNA within the membrane that surrounds the virus. However, antibodies against the N protein are also formed during infection with SARS-CoV-2 (15,16), and previous development of vaccines against SARS-CoV-1 has shown that the N protein can generate T cell responses that confer immunological memory (17). The inclusion of T cell epitopes located on the N protein may therefore be important for achieving immunity to COVID-19.

Vaccines against COVID-19

When the severity of the global threat posed by SARS-CoV-2 became apparent, multiple institutions, vaccine manufacturers and research groups engaged in the task of developing a vaccine. During the first few months of 2020 alliances and collaborations were established between major players in the vaccine industry, both in academia and in the commercial sector, and a number of vaccine candidates were launched. Several of the groups had previous experience with the development of vaccines against SARS-CoV-1 and MERS-CoV, and were able to quickly adapt these vaccines for use against SARS-CoV-2.

The WHO maintains a running list of candidate vaccines in development (18), and as of August 28th 2020, there were 142 registered vaccine candidates in the preclinical stage and an additional 31 in clinical trials (Table 1).

Table 1

Vaccine candidates registered by the WHO as being under clinical testing in August 2020, modified from reference 18 and links therein. Detailed information is not available for all vaccine candidates. All vaccines are administered via the intramuscular route with the exception of those by Inovio and Cadila, which are administered intradermally. S protein = spike protein, RBD = receptor binding domain, LNP = lipid nanoparticles

Manufacturer and vaccine type	Country	Vector / molecule	Antigen	Name	Phase 1	Phase 2	Phase 3
Non-replicating virus							
University of Oxford, AstraZeneca	UK	Chimpanzee adenovirus	S protein	AZD1222	x	x	x
CanSino Biological / Beijing Inst Biotech	China	Human adenovirus type 5	S protein	Ad5-nCoV	x	x	

Manufacturer and vaccine type	Country	Vector / molecule	Antigen	Name	Phase 1	Phase 2	Phase 3
Gamaleya Research Institute	Russia	Adenovirus (Ad5 and Ad26)	S protein	Sputnik V	x	x	
Janssen Pharmaceutical Companies	USA	Ad26COVS1	S protein		x		
ReiThera/LEUKOCARE/Univercells	Italy, Germany, Belgium	Chimpanzee adenovirus	S protein		x		
DNA- and RNA-based vaccine							
Moderna/NIAID	USA	LNP encapsulated mRNA	S protein	mRNA-1273	x	x	x
Imperial College London	UK	LNPnCoVsaRNA	S protein		x		
BioNTech/Fosun/Pharma/Pfizer	Germany, USA, and others	3 LNP-mRNAs	RBD	BNT162	x	x	x
Curevac	Germany	mRNA	S protein		x		
People's Liberation Army, Military Science,Walwax Biotech	China	mRNA-LNP	RBD	ARCoV	x		
Inovio Pharmaceuticals / IVI	USA	DNA plasmid	S protein	INO-4800	x	x	
Genexine Consortium	South Korea	DNA	S protein	GX-19	x		
Osaka University / AnGes / Takara Bio	Japan	DNA plasmid + adjuvant			x	x	
Cadila Healthcare Ltd	India	DNA plasmid		ZyCoV-D	x		
Arcturus/Duke-NUS	USA, Singapore	mRNA			x		
Protein subunit vaccine							
Novavax	USA	Glycoprotein nanoparticle	S protein	NVX-CoV23723	x	x	
Clover Biopharma Inc./GSK/ Dynavax	China, USA	Trimeric subunit S protein	S protein	SCB-2019	x		
Anhui Zhifei Longcom, Inst Microbiology China, CAS	China	RBD-dimer with adjuvant	RBD		x		
Vaxine Pty Ltd/Medytox	Australia, South Korea	S protein + Advax adjuvant	S protein		x		
University of Queensland / CSL Seqirus	Australia	Molecular clamp, S protein	S protein		x		
Medicago Inc.	Canada	Virus-like particle			x		
Kentucky Bioprocessing	USA	RBD-based	RBD		x		
Medigen Vaccine/NIAID/Dynavax	USA, Taiwan	S-2P protein + CpG 1018			x		
State Research Centre of Virology and Biotechnology VECTOR	Russia	Peptides (?)	EpiVacCorona		x		
Instituto Finlay de Vacunas	Cuba	RBD	RBD	Soberana 1	x		
Inactivated virus							
Wuhan Institute / Sinopharm	China	Inactivated SARS-CoV-2	Whole virus	COVID-19 vaccine	x	x	x
Beijing Institute of Biological Products / Sinopharm	China	Inactivated SARS-CoV-2	Whole virus	Sinovac	x	x	x

Manufacturer and vaccine type	Country	Vector / molecule	Antigen	Name	Phase 1	Phase 2	Phase 3
Sinovac	Kina	Inactivated SARS-CoV-2 + alum	Whole virus	CoronaVac	x	x	x
Inst. of Medical Biology, Chinese Academy of Med. Sciences	Kina	Inactivated SARS-CoV-2	Whole virus		x		
Bharat Biotech	India	Inactivated SARS-CoV-2	Whole virus		x	x	
Live, attenuated virus							
Institute Pasteur, Themis, Univ. of Pittsburg, Merck Sharp & Dome	France, USA	Measles virus, recombinant	S protein		x		

NON-REPLICATING VIRAL VACCINES

This type of vaccine is based on live virus that is unable to replicate in humans. In general, this type of vaccine gives rise to robust humoral and cellular immune responses. To prevent virus replication in humans one can either use a non-human virus or modify a human virus so that it is no longer able to replicate.

One of the most advanced vaccine candidates, which is now in phase 3 of clinical trials (Table 2) (19), is being developed as a collaboration between the University of Oxford in the UK and AstraZeneca, and goes by the name AZD1222. This vaccine uses a chimpanzee adenovirus as a vector (ChAdOx1) and has been modified to express the S protein from SARS-CoV-2. The adenovirus vector ChAdOx1 has previously been used in vaccine development against MERS, and a vaccine presenting the S protein from MERS was reported to be both safe and able to induce relevant immune responses (i.e. immunogenic) in a phase 1 trial (20). The vaccine research group thus had a platform available for the development of vaccines against coronaviruses and were able to quickly adapt this to SARS-CoV-2.

Table 2

Clinical phases of vaccine development (vaccine trials)

Stage	Goal	Primary outcome	Participants, typical numbers	Design
Phase 1	First time in humans, dose evaluation	Safety and immunogenicity[1]	Adult volunteers, 10–100 participants	Controlled or non-controlled
Phase 2	First evaluation in target population	Safety and immunogenicity	Target population, 50–500 participants	Randomised, double-blind, placebo-controlled
Phase 3	Full evaluation in target population	Protective effect, safety	Target population, 1 000–150 000 participants	Randomised, double-blind, placebo-controlled

[1]Able to induce measurable and relevant immune responses

Results from animal experiments have now shown that AZD1222 is immunogenic in mice and that rhesus monkeys (macaques) were protected against pneumonia following vaccination (21). Results from phase 1 and phase 2 clinical trials indicate that a single dose of vaccine can induce robust antibody responses, but that in some individuals vaccination will be accompanied by side effects such as transient fever, headache or pain at the injection site (22). The antibody data give cause for optimism regarding the vaccine's ability to generate protective immunity, and phase 3 trials are currently ongoing in England, India, Brazil, the USA and South Africa.

«What we won't know until the results of the phase 3 studies are available, however, is whether these immune responses provide protection against COVID-19»

Another vaccine candidate of this type is being developed in China by CanSino Biologics in collaboration with the Beijing Institute of Biotechnology. The vaccine uses human adenovirus type 5 as a vector, and has been modified to express the S protein from SARS-CoV-2. This vector has previously been used in the Ebola vaccine Ad5-EBOV (23), where it displayed a good safety profile in phase 1 and phase 2 trials. CanSino recently published results from a phase 1 trial with 108 participants for the vaccine against SARS-CoV-2. They found the vaccine to induce both neutralising antibodies and specific T cell responses (24). Like AZD1222, this vaccine also produced side effects such as pain at the injection site and fever, but no serious adverse events were reported. The strategy of using the

human common cold virus adenovirus type 5 as a vector has been criticised, as a proportion of the population can be expected to have pre-existing immunity to the vector and thus neutralise the vaccine before an immune response to the S protein is developed (23,25).

Another adenovirus-based vaccine is under development in Russia by the Gamaleya Research Institute of Epidemiology and Microbiology in Moscow. Little information is currently available, but the vaccine, *Sputnik V*, is said to have been through phase 1 and 2 trials, and a phase 3 trial has now been initiated. Sputnik V became the subject of controversy when Russia announced that the vaccine was the first in the world to be registered and approved, *before* a phase 3 trial had been conducted. Russian media are now reporting that a post-registration study is being carried out, in which tens of thousands of healthcare professionals have been enrolled.

NUCLEOTIDE VACCINES

Nucleotide vaccines consist of either DNA or RNA encoding the antigens to be expressed, and it is the cells of the human host that translate the nucleic acid sequences into viral proteins. Clinical studies over 20 years have shown nucleotide vaccines to be safe, but nevertheless no vaccines of this type have ever been approved for human use. This is because it is difficult to get nucleotide vaccines to generate immune responses strong enough to produce immunological memory. Despite this, ten of the 31 COVID-19 vaccines that have entered clinical trials are nucleotide vaccines. No other type of vaccine can be manufactured as quickly as a nucleotide vaccine, and the synthetic production process (involving no live virus or structural epitopes) is well suited for mass production. In recent years, major advances in vaccine delivery and vector design have increased confidence that nucleotide vaccines too can induce robust immunological memory. It is therefore possible that the SARS-CoV-2 pandemic may come to represent the breakthrough for the use of nucleotide vaccines in humans.

Detailed information is not available for all the nucleotide vaccines currently being tested, but most encode all or part of the S protein of SARS-CoV-2. Several of the vaccine manufacturers have previous clinical experience with this type of vaccine, targeting Ebola virus, Lassa virus, dengue virus and MERS. The potency of the immune responses that can be achieved with nucleotide vaccines remains unclear, and repeated doses may be required to achieve protective immune responses.

The nucleotide vaccine candidate that currently is the frontrunner is being developed by the biotechnology company Moderna in collaboration with the National Institutes of Health in the USA. The vaccine candidate consists of RNA encoding the S protein packaged inside lipid nanoparticles. The results of a phase 1 trial with 45 participants were recently published (26), and showed that the vaccine induced robust immune responses in participants. Side effects were also reported, however, especially for the highest dose, but none that were serious. The phase 2 trial has recently been completed, and recruitment of 30 000 individuals for a large phase 3 efficacy trial is ongoing.

Three other important players developing nucleotide-based vaccines are Inovio, Imperial College London and the German company CureVac. All three have extensive experience with their nucleotide-based vaccine platforms, and are well under way with clinical trials. To date, no clinical data have been published in the scientific literature.

PROTEIN SUBUNIT VACCINES

These vaccines consist of one or more proteins chosen because they are thought to be key antigens and thus to contain epitopes that may give rise to protective immunity. The fact that there is no need to work with live virus is an advantage with regard to manufacturing, and protein vaccines may be well-suited for mass production. However, care must be taken to ensure that vaccine proteins have the correct structure and folding to ensure that immune responses are induced against epitopes present naturally on the virus. Protein vaccines generally give rise to a weaker immune response than live vaccines, and repeated dosing and the addition of adjuvants will often be necessary to enhance the immune response.

At the time of writing ten protein vaccine candidates are in clinical trials, with the US company Novavax leading the field. Their vaccine candidate, which is also based on the S protein, has been tested in phase 1 studies in Australia and is now in phase 2. Also worth mentioning is the Canadian firm Medicago, which is producing a vaccine based on virus-like particles. These are protein-based structures that mimic the shape of a virus, but which lack the viral genome with the result that the virus cannot replicate. For the SARS-CoV-2 vaccine candidate, the proteins are produced in the leaves of a plant belonging to the tobacco family, and mimic the S protein of SARS-CoV-2. Medicago has experience with this vaccine platform from the development of influenza vaccines.

INACTIVATED VIRAL VACCINES

The principle of isolating a microbe and inactivating it in order to then inject it as a vaccine, was established by the vaccine pioneer Louis Pasteur in the nineteenth century. This approach has given us many of the vaccines in use today. Five manufacturers now have vaccine candidates in clinical trials where this principle has been applied to SARS-CoV-2. These vaccines contain antigens from the entire virus, but there is a risk that the inactivation process (which is usually chemical) may damage important epitopes. A challenge associated with the manufacturing process is that it requires working with large amounts of the pathogenic virus prior to inactivation, which can make it difficult to quickly and safely upscale vaccine production.

At the forefront of this group is the Chinese firm Sinovac, which has reached phase 3 in the testing of its vaccine candidate. The company has previous experience with vaccine development, including against SARS-CoV-1, and published promising early preclinical results for its SARS-CoV-2 vaccine candidate from animal experiments in mice, rats and non-human primates (27). No data from human studies have yet been published.

LIVE ATTENUATED VIRAL VACCINES

This type of vaccine is well-established and is used, for example, in the Norwegian child vaccination programme in the form of the MMR vaccine, which consists of attenuated measles virus (morbilli), mumps virus and rubella virus. The vaccine group at the Pasteur Institute has used attenuated morbilli virus as a vector to express the S protein of SARS-CoV-2, and this vaccine candidate is now in the first phase of clinical trials. A number of other vaccine candidates at the preclinical stage of development are using a similar strategy.

Vaccine development: other considerations

The development of a new vaccine is a highly complex and expensive process that usually takes many years, but which is currently taking place at unprecedented speed with many processes operating in parallel and with enormous financial support (28). Some important variables that must be studied for each vaccine candidate are the dose of antigen, dosing regimen, mode of administration and possible use of adjuvant. Also important are in-depth analyses of possible side effects, which are often closely related to vaccine dose. Here, there are limits on the extent to which the time frame can be compressed, as increased safety in terms of ruling out side effects is achieved through longer observation time and large phase 3 trials.

There are several examples of side effects that can pose a real challenge. The most feared is so-called antibody-mediated enhancement, in which vaccinated individuals may be at *increased* risk of serious illness if they become infected. Such an effect has been observed previously for vaccine candidates against respiratory syncytial virus (RSV) and dengue virus (29, 30). Animal experiments indicate that this may also be a challenge for the development of vaccines against coronaviruses (31–33). It is therefore important to test many different types of vaccines, preferably also with different antigens, to ensure that we can ultimately select effective vaccines that induce a safe immune response.

> *«The trend is increasingly towards development of universal vaccine platforms into which new antigens can quickly be integrated to produce a vaccine to counter a new epidemic threat»*

The upscaling and mass production of a vaccine is in itself a huge challenge when hundreds of millions, or possibly even billions, of doses are required. Precision and quality must be ensured at all stages, including appropriate transportation, storage and handling of the vaccine prior to it reaching the individual to be vaccinated. A political tug-of-war can be expected when the first doses of vaccine are to be distributed. Several international organisations will have an important role to play here, including the WHO, the vaccine alliance GAVI, and CEPI (the Coalition for Epidemic Preparedness Innovations). The latter, which was established in Norway and has its headquarters in Oslo, is providing major financial support to several of the leading vaccine candidates and is working to achieve a fair global distribution of vaccines. US authorities have launched a separate initiative called *Operation Warp Speed*, which is providing major financial support to selected vaccine candidates with the primary goal of securing US interests.

With respect to the various stages of clinical trials (Table 2), it should be noted that phase 1 studies are typically conducted in young, healthy adults, whereas it is the elderly who are most at risk of severe COVID-19. The elderly often also respond less well to vaccination. To date, clinical trials have primarily been performed in young adults, and therefore little is known about the effect of the various vaccines in the elderly. Although immune responses are evaluated in phase 1 and phase 2 trials, it is only in large-scale phase 3 trials that protection against disease is investigated.

CONCLUSION

The development of techniques for vaccination is one of the biggest and most important achievements in the history of medicine, at times so effective that we forget just how important vaccines are. In the face of the humanitarian and economic catastrophe that is now unfolding as a result of the ongoing pandemic, a huge amount of attention has been focused on the development of an effective vaccine against COVID-19, and great hopes have been pinned on its success. At the time of writing, at least 173 vaccine candidates are under development and six have entered phase 3 trials.

The picture so far is that several of the candidates have been judged safe enough for use in humans and have been shown to generate relevant immune responses towards SARS-CoV-2. What we will not know until the results of the phase 3 trials become available, however, is whether these immune responses provide protection against COVID-19. History has taught us that many promising vaccine candidates disappoint when their protective effect is evaluated in large clinical trials. As for the duration of immunity, we can at present only speculate.

> *«Several candidates have been judged safe enough for use in humans and have been shown to generate relevant immune responses towards SARS-CoV-2»*

The achievements of the last six months in the vaccine field have shown that when the need is great enough and the global community focuses its efforts on a single defined goal, processes that usually take many years can be compressed into a few months. This is partly because regulatory authorities have given the matter top priority, and partly because of the enormous financial resources available and a willingness to take financial risks.

However, another key reason is the so-called 'platform technologies' used by the vaccine industry. The trend is increasingly towards the development of universal vaccine platforms into which new antigens can quickly be integrated to counter a new epidemic threat.

If there is one thing the pandemic has taught us, it is that investing in epidemic preparedness should be a top priority if we are to maintain the way of life, standard of living and freedom of movement we all desire. The pandemic caused by SARS-CoV-2 is not the first, and will certainly not be the last, to hit mankind. The viruses will keep on coming, and the solution will often be a vaccine.

This article has been peer-reviewed.

LITERATURE

1. World Health Organization. WHO announces COVID-19 outbreak a pandemic. https://www.euro.who.int/en/health-topics/healthemergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic Accessed 2.9.2020.

2. Zhou P, Yang XL, Wang XG et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579: 270–3. [PubMed][CrossRef]

3. Folkhälsomyndigheten. Förekomsten av covid-19 i Sverige 21–24 april och 25–28 maj 2020. https://www.folkhalsomyndigheten.se/publicerat-material/publikationsarkiv/f/forekomsten-av-covid-19-i-sverige-21-24-april-och-25-28maj-2020/ Accessed 2.9.2020.

4. Pollán M, Pérez-Gómez B, Pastor-Barriuso R et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. Lancet 2020; 396: 535–44. [PubMed][CrossRef]

5. Grifoni A, Weiskopf D, Ramirez SI et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. Cell 2020; 181: 1489–1501.e15. [PubMed][CrossRef]

6. Shereen MA, Khan S, Kazmi A et al. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res 2020; 24: 91–8. [PubMed][CrossRef]

7. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol 2015; 1282: 1–23. [PubMed][CrossRef]

8. Christian MD, Poutanen SM, Loutfy MR et al. Severe acute respiratory syndrome. Clin Infect Dis 2004; 38: 1420–7. [PubMed][CrossRef]

9. Chafekar A, Fielding BC. MERS-CoV: Understanding the Latest Human Coronavirus Threat. Viruses 2018; 10: 93. [PubMed][CrossRef]

10. Wu A, Peng Y, Huang B et al. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe 2020; 27: 325–8. [PubMed][CrossRef]

11. Wang Y, Anirudhan V, Du R et al. RNA-dependent RNA polymerase of SARS-CoV-2 as a therapeutic target. J Med Virol 2020; jmv.26264.

12. Hoffmann M, Kleine-Weber H, Schroeder S et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181: 271–280.e8. [PubMed][CrossRef]

13. Hofmann H, Pyrc K, van der Hoek L et al. Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry. Proc Natl Acad Sci U S A 2005; 102: 7988–93. [PubMed][CrossRef]

14. Yan R, Zhang Y, Li Y et al. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 2020; 367: 1444–8. [PubMed][CrossRef]

15. To KK, Tsang OT, Leung WS et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis 2020; 20: 565–74. [PubMed][CrossRef]

16. Sun B, Feng Y, Mo X et al. Kinetics of SARS-CoV-2 specific IgM and IgG responses in COVID-19 patients. Emerg Microbes Infect 2020; 9: 940–8. [PubMed][CrossRef]

17. Peng H, Yang LT, Wang LY et al. Long-lived memory T lymphocyte responses against SARS coronavirus nucleocapsid protein in SARS-recovered patients. Virology 2006; 351: 466–75. [PubMed][CrossRef]

18. World Health Organization. Draft landscape of COVID-19 candidate vaccines. https://www.who.int/publications/m/item/draftlandscape-of-covid-19-candidate-vaccines Accessed 28.8.2020.

19. Farrington CP, Miller E. Vaccine trials. Mol Biotechnol 2001; 17: 43–58. [PubMed][CrossRef]

20. Folegatti PM, Bittaye M, Flaxman A et al. Safety and immunogenicity of a candidate Middle East respiratory syndrome coronavirus viral-vectored vaccine: a dose-escalation, open-label, non-randomised, uncontrolled, phase 1 trial. Lancet Infect Dis 2020; 20: 816–26. [PubMed][CrossRef]

21. van Doremalen N, Lambe T, Spencer A et al. ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques. bioRxiv 2020; 2020.05.13.093195.

22. Folegatti PM, Ewer KJ, Aley PK et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet 2020; 396: 467–78. [PubMed][CrossRef]

23. Wu L, Zhang Z, Gao H et al. Open-label phase I clinical trial of Ad5-EBOV in Africans in China. Hum Vaccin Immunother 2017; 13: 2078–85. [PubMed][CrossRef]

24. Zhu FC, Li YH, Guan XH et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. Lancet 2020; 395: 1845–54. [PubMed][CrossRef]

25. Sekaly RP. The failed HIV Merck vaccine study: a step back or a launching point for future vaccine development? J Exp Med 2008; 205: 7–12. [PubMed][CrossRef]

26. Jackson LA, Anderson EJ, Rouphael NG et al. An mRNA vaccine against SARS-CoV-2 — Preliminary report. N Engl J Med 2020; 383: NEJMoa2022483.

27. Gao Q, Bao L, Mao H et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science 2020; 369: 77–81. [PubMed][CrossRef]

28. Heaton PM. The Covid-19 vaccine-development multiverse. N Engl J Med 2020; 383: NEJMe2025111.

29. Acosta PL, Caballero MT, Polack FP. Brief history and characterization of enhanced respiratory syncytial virus disease. Clin Vaccine Immunol 2015; 23: 189–95. [PubMed][CrossRef]

30. Huisman W, Martina BEE, Rimmelzwaan GF et al. Vaccine-induced enhancement of viral infections. Vaccine 2009; 27: 505–12. [PubMed][CrossRef]

31. Weiss RC, Scott FW. Antibody-mediated enhancement of disease in feline infectious peritonitis: comparisons with dengue hemorrhagic fever. Comp Immunol Microbiol Infect Dis 1981; 4: 175–89. [PubMed][CrossRef]

32. Coish JM, MacNeil AJ. Out of the frying pan and into the fire? Due diligence warranted for ADE in COVID-19. Microbes Infect 2020; S1286-4579(20)30124-6.

33. Ulrich H, Pillat MM, Tárnok A. Dengue Fever, COVID-19 (SARS-CoV-2), and Antibody-Dependent Enhancement (ADE): A Perspective. Cytometry A 2020; 97: 662–7. [PubMed][CrossRef]

Publisert: 9 September 2020. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.20.0676
Received 25.8.2020, first revision submitted 30.8.2020, accepted 2.9.2020.