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Editorial

Vaccines against COVID-19

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Vaccination is one of the most effective medical interventions ever implemented in human history and has contributed significantly to the decrease of infectious disease burden in many countries. The success of vaccination is such that today many citizens regard infectious diseases as plagues of the past which have basically disappeared, and some question the utility of continuous large-scale vaccination. However, discontinuing high-coverage vaccination results in an almost immediate rebound [1]. Despite the undeniable success of vaccines, new pandemics starting towards the end of the 20th century, such as Acquired Immune-Deficiency Syndrome (AIDS), or the beginning of the 21st century, such as the new Coronavirus disease-19 (COVID-19), illustrate that infections still represent significant threads to mankind. For both diseases no vaccine is yet available, leaving us with physical protection and/or social distancing as the only preventive measures.

Difficulties in developing vaccines against new pandemics

While enormous efforts have been deployed since decades to develop vaccines against AIDS, several promising anti-COVID-19 vaccines are after less than one year already in late stage clinical development. This high-speed development is largely due to strong commitments of academia, industry and politicians, and to massive financial resources for vaccine projects. While most anti-COVID-19 vaccine candidates target the spike protein (S) of the SARS-COV-2 virus aiming at inducing neutralising antibodies, a major concern is the risk of inducing disease-enhancing antibodies. The generation of disease-enhancing antibodies has been a major hurdle for vaccine development against Respiratory Syncytial Virus (RSV) [2] and dengue [3].

The duration of immunity to COVID-19 induced by infection or vaccination is not known, and some reports suggest that antibody-mediated immunity may last for only a few months [4]. As neutralising antibody titres wane, remaining non-neutralising antibodies may enhance disease by facilitating viral entry into Fcγ receptor-bearing cells. Although this has not yet been shown for SARS-CoV-2 [5], it has been demonstrated for dengue [3]. One way to overcome this potential risk is to include antigens/epitopes that generate cell-mediated immunity, particularly via $CD8^+$ T cells. This has been proven protective against dengue, even in the presence of disease-enhancing antibodies [6]. Especially tissue-resident memory $CD8^+$ T cells generated in the upper airways may be important for long-lasting protection, as has been shown for influenza [7].

Anti-COVID-19 vaccines in clinical development

Several hundred COVID-19-specific vaccines are at various stages of development in academia and industry and make use of a variety of different generic platforms, such as inactivated virus, purified recombinant viral proteins with or without adjuvant, replicating and non-replicating viral vectored antigens, antigen-encoding DNA or mRNA. Some of them build on technologies approved for other vaccines, others are novel and have not yet been used for large-scale vaccination. This editorial will focus on vaccines in clinical development with data published in peer-reviewed articles (Table 1).

Adenovirus-vectored vaccines

The first clinical trial data were published in June 2020 [8]. The trial was a dose-escalation study of recombinant adenovirus type-5 vectored S. The vaccine was shown tolerable, although 75–83% of participants reported adverse events, mostly mild or moderate. It induced neutralising antibody and T cell responses with seroconversion in 50–75% of the vaccine recipients. However, pre-existing vector-neutralising antibodies diminished the immune responses. Furthermore, immunogenicity was sub-optimal in older participants. This study was followed by a phase 2, randomised, double-blind trial [9], including 508 participants. Sero-conversion was seen in more than 95% and neutralising antibodies were generated in 85% of vaccine recipients. IFN-γ responses were also seen in roughly 90% of the vaccinees. Again, the vaccine induced lower antibody responses in older participants and subjects with pre-existing anti-vector immunity. The vaccine at a 5×10^{10} viral particles/mL dose is now in a phase 3 trial in Brazil.

To overcome the immune-interference by pre-existing immunity to the vector, a replication-deficient simian adenovirus-vectored vaccine was engineered to encode S. A phase 1/2, single-blind, randomised controlled study with this vaccine at 5×10^{10} viral particles/mL in 1077 healthy adults showed acceptable safety [10]. Local and systemic reactions were frequent but could be

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Table 1
Anti-COVID-19 vaccines in advanced clinical development[1].

Origin	Platform	Dose	Development stage	References
China	Ad5[2]	5×10^{10} VP[3]	Phase 3 ongoing	8, 9
UK	ChAdOx[4]	5×10^{10} VP	Phase 3 ongoing	10
Russia	As26[5]/Ad5	10^{11} VP	Phase 1/2 completed	11
China	whole virus	2×5 μg	Phase 3 ongoing	14
Germany	mRNA	30 μg	Phase 3 ongoing	15, 16
USA	mRNA	100 μg	Phase 3 ongoing	17, 18

[1] Only vaccines for which clinical data were published in peer-reviewed articles are listed.
[2] Adenovirus type-5-vectored vaccine.
[3] VP, viral particles.
[4] Chimpanzee adenovirus-vectored vaccine.
[5] Adenovirus type-26-vectored vaccine.

reduced by paracetamol. The vaccine also induced T cell and antibody responses, including virus-neutralising antibodies. After a booster given to some participants, antibody responses and increased neutralising antibodies were generated in all participants. This vaccine is currently in phase 3 in several countries.

A combination of two adenovirus-vectored vaccines (types 26 and 5), both carrying S, was tested in a non-randomised, non-placebo-controlled phase 1/2 trial in a total of 38 volunteers in Russia [11]. In phase 1, each vaccine was tested individually, followed by phase 2, in which the participants were primed with rAd26 and boosted with rAd5. The two studies combined included 38 volunteers. Adverse events included injection-site pain in 58% of the participants, as well as hyperthermia, headache, asthenia, and muscle and joint pain. All participants generated high titres of IgG recognising the receptor-binding domain of S. Neutralising titres were also induced, as well as $CD4^+$ and $CD8^+$ T cell responses. Although safety and immunogenicity reported in this study were in line with the previous studies on adenovirus-vectored vaccines, this study has raised concerns about the validity of the reported results, especially in the context of potential accelerated distribution of the vaccine in the population in Russia [12].

Inactivated whole-virus vaccines

An inactivated, alum-adjuvanted whole-virus vaccine has also undergone a phase 1/2 trial [13]. In phase 1 with 96 participants, three intramuscular injections of 2.5, 5 and 10 μg/dose were compared to alum, followed by phase 2 with 224 participants comparing two injections of 5 μg/dose with alum. Adverse reactions, mild and self-limiting injection site pain and fever occurred in 9–20.8% of vaccine recipients and were not more frequent than in the alum control group. The geometric mean titres of neutralising antibodies ranged from 121 to 316.

mRNA-based vaccines

Two RNA-based vaccines are currently in phase 3, mRNA-1273 and BNT162b2, with the aim of showing at least 50% efficacy. BNT162b1 is a lipid-nanoparticle-formulated, nucleoside-modified mRNA encoding the receptor-binding domain of S. A phase 1/2 placebo-controlled, dose-escalation study on 45 adults, randomised to receive 2 doses of 10, 30 or 100 μg showed dose-dependent reactogenicity [14]. Antibodies recognising the receptor-binding domain and neutralising antibodies were also elicited in a dose-dependent manner and increased after a second dose. This vaccine was subsequently compared to a second version, BNT162b2, encoding stabilised, membrane-anchored full-length prefusion S [15]. Interestingly, both vaccines elicited similar dose-responses in younger and older adults, and BNT162b2 was selected for further clinical development because of improved safety.

Similarly, mRNA-1273 also codes for stabilised prefusion S. A phase 1, open-label trial in young adults showed acceptable safety and reactogenicity and the induction of neutralising antibodies after two injections [16]. This vaccine was also tested for safety in older adults, age 56–70 and above [17], using two doses of 25 μg or 100 μg. In this population, adverse events were moderate for both dosages, but the 100-μg dose was chosen because it induced stronger neutralising antibody titres. The vaccine also induced $CD4^+$ T cell responses, including IFN-γ, IL-2 and TNF-α production.

In addition to these studies, more than 200 trials have been registered so far on ClinicalTrials.gov (https://clinicaltrials.gov/ct2/results?term=COVID-19+vaccine&Search=Search), but safety, efficacy or immunogenicity data are lacking for most of them. Besides SARS-CoV-2-specific vaccines, these trials also include studies on heterologous vaccines, in particular the Bacillus Calmette-Guérin (BCG). BCG is known to induce heterologous protection, especially against respiratory infections, by the generation of trained innate immunity, and may therefore potentially protect against COVID-19 [18].

Conclusion

Vaccines take usually at least 10–15 years to be developed due to the phasing of vaccine development, from pre-clinical to clinical phases 1, 2 and 3, the latter being the conclusive efficacy trial. These phases are usually conducted sequentially, as they become increasingly costly. Therefore, before engaging resources to the following phase, it is important to ensure that the data of the previous phase are convincing enough to warrant further development. Anti-COVID-19 vaccine development has proceeded at an unprecedented pace, as several phases are conducted simultaneously because of massive financial resources poured into vaccine development. Within months rather than years, more than 30 vaccines have entered the clinical development pipeline, including a dozen in phase 2/3 trials. Simultaneously, large-scale manufacturing was launched before data on safety and efficacy were gathered to make safe and effective vaccines readily available. However, considering the width of the COVID-19 pandemic, mounting to more than 1,000,000 global deaths at the time this article was prepared, it remains uncertain whether enough vaccines will be available. Vaccine roll out will take time and is accompanied by difficult decisions about priorities as to who should receive the vaccines first [19]. Furthermore, accelerated vaccine development may also lead to confusion in the public perception and concern about safety and efficacy of anti-COVID-19 vaccines once approved, and about vaccines in general [20]. Furthermore, there is a risk that anti-vaccine movements will use this opportunity to strengthen their position, which may have disastrous consequences, as vaccine hesitancy is regarded as one of the 10 most important global health threats today. Yet, the widespread use of safe and efficacious anti-COVID-19 vaccine is the only hope for us to return to a “normal” life.

Conflicts of interest

None.

References

[1] Rowani P, Zhong X, King AA. Contact network structure explains the changing epidemiology of pertussis. Science 2010;330:982–5.
[2] Anderson LJ, Heilman CA. Protective and disease-enhancing immune responses to respiratory syncytial virus. J Infect Dis 1995;171:1–7.
[3] Libraty DH, Endy TP, Houng HS, Green S, Kalayanarooj S, Suntayakorn S, et al. Differing influences of virus burden and immune activation on disease severity in secondary dengue-3 virus infection. J Infect Dis 2002;185:1213–21.

[4] Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med 2020;26:1200–4.
[5] Arvin AN, Fink K, Schmid MA, Cathcart A, Spreafico R, Havenar-Daughton C, et al. A perspective on potential antibody-dependent enhancement of SARS-CoV-2. Nature 2020;584:353–63.
[6] Lam JH, Chua YL, Lee PX, Martínez Gómez JM, Ooi EE, Alonso S. Dengue vaccine-induced CD8+ T cell immunity confers protection in the context of enhancing, interfering maternal antibodies. J Clin Invest Insight 2017;2:e94500.
[7] Pizzolla A, Nguyen THO, Smith JM, Brooks AG, Kedzieska K, Heath WR, et al. Resident memory CD8+ T cells in the upper respiratory tract prevent pulmonary influenza virus infection. Sci Immunol 2017;2:eaam6970.
[8] Zhu FC, Li YH, Guan XH, Hou LH, Wang WJ, Li JX, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomized, first-in-human trial. Lancet 2020;395:1845–54.
[9] Zhu FC, Guan XH, Li YH, Huang JY, Jiang T, Hou LH, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomized, double-blind, placebo-controlled, phase 2 trial. Lancet 2020;396:479–88.
[10] Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, 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, randomized controlled trial. Lancet 2020;396:467–78.
[11] Logunov DY, Dolzhikova IV, Zubkova OV, Tukhvatullin AI, Shcheblyakov DV, Dzharullaeva AS, et al. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. Lancet 2020;396:887–97.
[12] Caddy S. Russian SARS-CoV-2 vaccine. Br Med J (Clin Res Ed) 2020;370:m3270.
[13] Xia S, Duan K, Zhang Y, Zhao D, Zhang H, Xie Z, et al. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes, Interim analysis of 2 randomized clinical trials. JAMA 2020;324:951–60.
[14] Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults. Nature 2020;586:589–93. in press.
[15] Walsh EE, Frenck R, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. RNA-based COVID-19 vaccine BNT162b2 selected for a pivotal efficacy study. medRxiv 2020, https://doi.org/10.1101/2020.08.17.20176651.
[16] Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA vaccine against SARS-CoV-2 – preliminary report. N Engl J Med 2020. in press.
[17] Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med 2020. in press.
[18] O'Neill LAJ, Netea MG. BCG-induced trained immunity: can it offer protection against CIVD-19? Nat Rev Immunol 2020;20:335–7.
[19] Mahase E. Covid-19: vaccine roll out could take a year and will require difficult priority decisions. BMJ 2020;371:m3846.
[20] Bauchner H, Malani PN, Sharfstein J. Reassuring the public and clinical community about the scientific review and approval of a COVID-19 vaccine. JAMA 2020. in press.

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