Biotechnology and Bioprocess Engineering 27: 461-467 (2022)
DOI 10.1007/s12257-022-0188-4

pISSN 1226-8372
eISSN 1976-3816

INVITED REVIEW PAPER

Current Updates on COVID-19 Vaccines and Therapeutics: As of June 2022

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Received: 24 June 2022 / Revised: 29 June 2022 / Accepted: 29 June 2022

Abstract Since COVID-19, caused by SARS-CoV-2 infection, has become a global issue, many vaccines and therapeutic candidates have been developed or are being developed against the COVID-19 endemic and the next wave. However, it is difficult to overcome the spread and mutation rate of SARS-CoV-2 in the COVID-19 pandemic because development of vaccines and therapeutics involves considerable social cost and time, as well as research capabilities. Thus, assessing the development status of these agents is important for advancing efficient research strategies. In this review, we summarize the status of 141 vaccines and 345 therapeutic candidates under development worldwide, according to their development stage and characteristics. As of June 2022, 32 vaccines and 12 therapeutics have been approved for emergency use. Although the development of four of these therapeutics was terminated owing to their low efficacy against various variants of SARS-CoV-2, many new candidates that have completed phase 3 clinical trials have been awaiting phase 4 clinical trials or full approval by the Food and Drug Administration (FDA). These efforts are expected to contribute to establishing an efficient research strategy to overcome the COVID-19 pandemic and facilitate its transition toward an endemic phase.

Keywords: COVID-19, SARS-CoV-2, vaccine, therapeutics

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic is the hottest global topic of 2020-2022, and it shook the political, economic, cultural, and public healthcare fields worldwide. SARS-CoV-2 (SCoV2) primarily infects the upper respiratory tract and exhibits gradual dissemination to multiple organs such as the lung, liver, kidney, heart, spleen, and brain, following various symptoms after an infection period of approximately 3-5 days [1-3]. Although the incubation period and fatality fluctuate according to its genomic variants, SCoV2 has shown an average fatality of approximately 1.18% (cumulative deaths/cases: 6,314,972/535,863,950, as of June 22, 2022) over the past two years [4]. Compared to previous coronaviruses, SCoV2 poses a serious threat to human health over a long period of time because of a higher transmission rate (reproductive number of SCoV:SCoV2 = 1.77:2.9) with lower fatality (SCoV, 15%; MERS, 37%) [5,6].

After the rapid spread of the omicron variant around the world, the cases of infections and deaths temporarily increased; however, it is now gradually decreasing. However, the health and economic damage accumulated by the COVID-19 pandemic continues to increase, and it is unknown whether new fatal variants will develop. In this situation, research institutes and companies around the world are developing and verifying numerous vaccine and therapeutic candidates to overcome the threat of COVID-19. Several vaccine and therapeutic candidates are at final stages of development worldwide, and new candidates are frequently added to the pipeline [7,8]. However, compared to the rapid spread of SCoV2 and the occurrence of mutations, the enormous social cost and long time required for discovering the candidates, evaluating efficacy, and researching side effects are onerous. Therefore, for

establishing an efficient research and development strategy to overcome COVID-19, it is necessary to summarize and review the current status of vaccines and therapeutic candidates under development.

In this review, we have summarized and listed various candidates currently under development by platform and clinical stage and highlighted notable candidates. Particularly, we also provided updated information regarding vaccines and therapeutics which are clinically available for COVID-19 patients infected with various SCoV2 variants including omicron variant, as of June 2022. This review can contribute to ongoing research and further can provide future direction to combat COVID-19 endemic and emerging infectious diseases.

2. Vaccine

As of June, 2022, a total of 163 vaccine candidates are being studied in the clinical stage, of which 156 candidates are being verified by various institutions and 7 are no longer in clinical development owing to issues faced by the developers [7,9]. We classified and listed 163 vaccine candidates according to their platform, clinical stage, and route of administration (Fig. 1, Table S1).

Most candidates are recombinant protein subunit vaccines (54 candidates; 33.1%), followed by mRNA (29), non-replicating viral vectors (29), and inactivated viruses (21) (Table 1).

Thirty-five candidates have been approved in at least

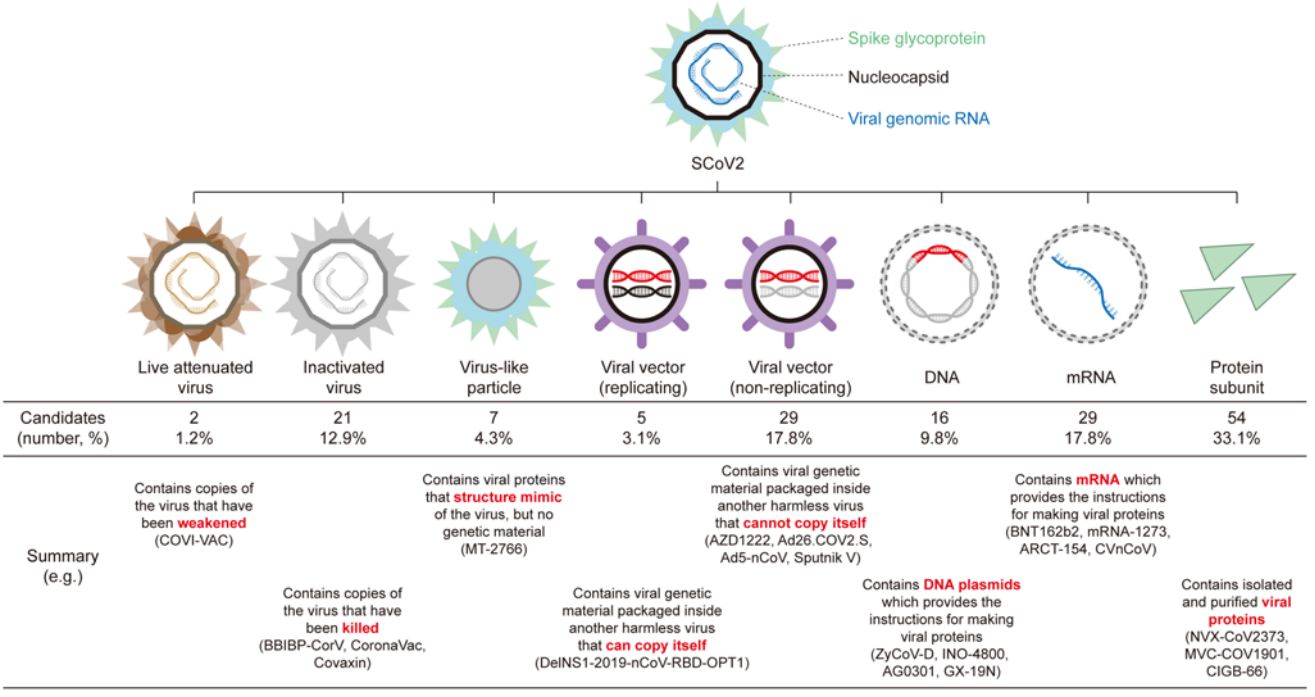

Fig. 1. An overview of vaccine platforms targeting SARS-CoV-2. The characteristics and share of the eight types of platforms currently being developed are summarized and displayed. Representative candidates are listed.

Table 1. Current statistics of SARS-CoV-2 vaccine candidates in clinical trials (May 15, 2022)

Platform	Number of candidates	%	Reported (approved[a]) phase			
			Phase 1	Phase 2	Phase 3	Phase 4
Protein subunit	54	33.1	11	16 (1)	26 (11)	1 (1)
mRNA	29	17.8	10	10 (1)	6	3 (2)
Viral vector (non-replicating)	29	17.8	10	10	6 (3)	3 (3)
Inactivated virus	21	12.9	6	2 (1)	10 (7)	3 (3)
DNA	16	9.8	6	6	4 (1)	
Virus-like particle	7	4.3		5	2 (1)	
Viral vector (replicating)	5	3.1	1	2	2	
Live attenuated virus	2	1.2	2			
Total	163	100	46	51 (3)	56 (23)	10 (9)

[a]Vaccines approved by at least one country.

one country. They include 13 protein subunit vaccines, 11 inactivated virus vaccines, 6 non-replicating viral vectors (5, when Covishield is considered the same as AZD1222), 3 mRNA vaccines (2, when TAK-919 is considered the same as mRNA-1273), 1 DNA vaccine, and 1 virus-like particle (VLP) vaccine. Nine vaccines have progressed to phase 4, and the inactivated virus vaccines, non-replicating viral vector vaccines, and mRNA vaccines, which were urgently approved by emergency use authorization (EUA) in the early stages of the pandemic, have preferentially progressed to phase 4.

Among the 66 candidates in phases 3 and 4, 62 candidates occupy the majority as intramuscular (IM) injection type, which is not related to the vaccine platform and is considered to be convenient for development and manufacturing. This judgment is based on the fact that the platforms of candidates selected for intranasal (IN), subcutaneous (SC), or oral administration types are not biased and are being developed on several platforms, although there are doubts about its effectiveness, as it is only in phase 1 and 2.

2.1. Inactivated virus

Twenty-one inactivated virus candidates are under development, only 12.9% of the total; however, the number of candidates in phases 3 and 4 and with emergency approvals was higher than those based on other platforms (Table 1).

Most approved vaccine candidates, including those in phases 3 and 4, have been developed mainly in Asian countries such as China. BBIBP-CorV (Sinopharm) and CoronaVac (Sinovac Research and Development), which were developed in China at the beginning of the pandemic, have been approved and utilized in 90 and 54 countries, respectively. Covaxin (Bharat Biotech International), developed in India, has also been approved in 14 countries. QazVac (Research Institute for Biological Safety Problems, Rep of Kazakhstan), KCONVAC (Minhai Biotechnology, China), ERUCOV-VAC (Erciyes University, Turkey), FAKHRAVAC (Organization of Defensive Innovation and Research, Iran), COVIran Barekat (Shifa Pharmed Industrial, Iran), and KoviVac (Chumakov Federal Scientific Center, Russia) have been approved and are used mainly in the countries where they were developed.

2.2. Viral vector

AZD1222 (AstraZeneca), Ad26.COV2.S (Janssen Pharmaceutical), and Ad5-nCoV (CanSino Biological) have completed phase 4, and AZD1222 has been approved in 138 countries, making it the most approved vaccine currently in many countries, along with the mRNA vaccine BNT162b2 (Pfizer/BioNTech). Ad26.COV2.S has been approved in 108 countries, and Sputnik V (Gamaleya Research Institute), which has completed phase 3, has been widely used in 74 countries. Covishield (Serum Institute of India), the same formulation as AZD1222, has been approved and used in 47 countries. Non-replicating viral vector candidates that have completed phases 3 and 4 are based on adenovirus vectors, and candidates using other virus-derived vectors, such as the modified vaccinia virus Ankara (MVA) and Newcastle disease virus (NDV), are completing phase 2 one after another (Table S1).

Few candidates based on replicating viral vector platforms are under development. Among them, DelNS1-2019-nCoV-RBD-OPT1 (Beijing Wantai Biological Pharmacy) is a notable replicating viral vector vaccine that uses an influenza virus vector; among candidates that have completed phase 3, it is an unusual candidate to be administered as an IN spray [10,11].

AZD2816 was developed for targeting the beta variant of SCoV2; although it has passed phase 3, the importance of its development has decreased because the omicron variant has become the predominant variant worldwide.

2.3. DNA

ZyCoV-D (Zydus Cadila) is the only candidate on the DNA platform that has been approved (EUA, phase 3 completed) and is administered by three injections through the intradermal route. In addition, INO-4800 (Inovio Pharmaceuticals), AG0301 (AnGes), and GX-19N (Genexine) completed phase 3. Unfortunately, it was recently announced that GX-19N is no longer being developed because of its low business value and developmental circumstances [12].

2.4. mRNA

Among mRNA vaccines, BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (ModernaTX), which completed phase 4 after emergency approval, are the most representative and are currently widely used with approval in 141 and 85 countries, respectively.

ModernaTX is considered the most advanced among the mRNA vaccines; phase 3 development has been completed for booster shots of mRNA-1273.211 (a 1:1 mixture of mRNA-1273 and mRNA-1273.351 that target the beta variant) and mRNA-1273.529 (targeting the omicron variant) [13,14]. ModernaTX derived the remarkable clinical results for the beta and omicron variants based on rapid preclinical studies of these booster shots [15,16]. Furthermore, mRNA-1283 has progressed to phase 2 trials; this candidate encodes a shorter antigen than mRNA-1273 and exhibits better thermostability during storage [17,18].

Arcturus Therapeutics developed ARCT-154 (phase 3) and ARCT-021 (phase 2) and announced a booster shot of ARCT-165 (phase 2) in response to several variants of SCoV2. In addition, the development of CVnCoV (CureVac)

and MRT5500 (Sanofi Pasteur/Translate Bio) progressed to phase 3 and phase 2, respectively; however, it was suspended owing to issues faced by the developer, such as low marketability [19,20].

2.5. Protein subunit

This platform has the largest number of candidates in clinical trials; 27 candidates have completed phase 3 or more, and the number of urgently approved vaccines has been has been rising rapidly since 2022. However, with the exception of NVX-CoV2373 (Novavax), they have not been approved worldwide and they tend to be used only in the country of their origin or developing countries (Table S1).

NVX-CoV2373 has been currently approved by the EUA in 37 countries, and it is available for use. COVOVAX (Serum Institute of India), the same formulation as NVX-CoV2373, is used in four countries, therefore, it is considered the leading vaccine on the protein subunit platform.

MVC-COV1901 (Medigen Vaccine Biologics, Taiwan) is the only protein subunit vaccine that has completed phase 4 since receiving EUA; however, EUA approval was only received in Taiwan and two other countries [21,22]. Similarly, the following vaccines, which have received local approval, are used locally: CIGB-66 (Center for Genetic Engineering and Biotechnology, Cuba and other Latin American countries), FINLAY-FR-1/FINLAY-FR-2 (Instituto Finlay de Vacunas, Cuba and other Latin American countries), Zifivax (Anhui Zhifei Longcom Biopharmaceutical, China), Spikogen (Vaxine/CinnaGen, Iran), Razi Cov Pars (Razi Vaccine and Serum Research Institute, Iran), Noora (Bagheiat-allah University of Medical Sciences, Iran), EpiVacCorona (FBRI VECTOR State Research Center of Virology and Biotechnology, Russia), BECOV2 (Biological E, India), and NVSI-06-08 (National Vaccine and Serum Institute, China and United Arab Emirates).

Unfortunately, the development of the protein subunit vaccines against new variants is inevitably delayed compared to the mRNA platform owing to procedural differences in vaccine development. Although SII B.1.351, SII Bivalent (each targeting the beta variant) and SII B.1.617.2 (targeting the delta variant) vaccines of Novavax still remains in phase 2 clinical trials, NVX-CoV2515 as a booster shot against the omicron variant has quite recently completed phase 3 (May 2022) [23,24].

2.6. Other platforms

Compared to the platforms mentioned above, other platforms have few candidates overall and fewer notable candidates. MT-2766 (Medicago), a plant-based VLP vaccine, has completed phase 3 through multinational clinical trials and approved in Canada [25].

3. Therapeutics

Among the therapeutics listed in the 'Therapeutics tracker of BioRender 2021 [26]' and 'COVID-19 EUA information of FDA [27]', we classified and listed drug candidates undergoing clinical trials as of May 2022, except convalescent plasma products.

We classified a total of 352 drug candidates according to target characteristics and mechanisms of action and found that the representative strategies involve reducing the fatality rate by suppressing inflammation, direct administration of antibodies against the spike protein of SCoV2, inhibiting intracellular entry of SCoV2, or inhibiting virus proliferation by targeting SCoV2 protease or polymerase (Table S2). Among them, we focused on analyzing drugs that have completed phase 3 and 4 development with relatively well-established data on efficacy and mechanism.

Because it usually takes a long time (typically over 10 years) to develop, clinical, and approve drugs in the biotherapeutic field, developing novel drugs from the preclinical stage was difficult after SCoV2 already became a pandemic. Therefore, early development activities have focused on drug repurposing plan. Among the 147 drug candidates that have completed phases 3 and 4, 67 have already been approved by the Food and Drug Administration (FDA) for other purposes (71 drugs including those only approved in countries other than the USA) (Table S2) [26].

There are 24 antiviral candidates, which have been developed as therapeutic agents targeting other viruses or pan-viruses, except Ensovibep (Novartis). Ensovibep, a multi-specific designed ankyrin repeat protein (DARPin), inhibits SCoV2 infection through a mechanism that neutralizes the epitope region of the SCoV2 spike glycoprotein [28].

There are 33 antibody candidates, 11 of which target the spike glycoprotein of SCoV2; the rest are antibodies that target key proteins involved in hyperinflammation.

As of May 2022, the nucleotide analog Remdesivir (Gilead) has been approved only by the FDA, and the 11 drugs listed below have been granted EUA for SCoV2 (Table 2) [27]. Paxlovid (Pfizer) consists of Nirmatrelvir and Ritonavir tablets, viral protease inhibitors, which are co-packaged for oral use. Molnupiravir (Merck Sharp & Dohme) was based on the nucleoside derivative N4-hydroxycytidine. Both Baricitinib (Nova Scotia Health Authority), an inhibitor of JAK1/2, and Tocilizumab (Roche), an antibody against IL-6R, were approved under EUA as drugs for suppressing immune responses following SCoV2 infection. These two antibodies have been approved by the FDA for autoimmune diseases, such as rheumatoid arthritis. In addition, the FDA has granted EUA to six antibody drugs against the spike glycoprotein of SCoV2: Casirivimab/

Table 2. SARS-CoV-2 drug candidates authorized for emergency use (May 15, 2022)

Candidate	Platform	Target of function	Developer	FDA approved previously	Authorization
Remdesivir	Antiviral	Nucleotide analog	Gilead		Approved for SARS-CoV-2
Chloroquine	Other	Lowering of endosomal pH	Multiple Organizations	O	EUA was revoked[a]
Nirmatrelvir/Ritonavir (Paxlovid)	Antiviral	Protease inhibitor	Pfizer		EUA
Molnupiravir	Antiviral	Nucleoside derivative N4-hydroxycytidine	Merck Sharp & Dohme		EUA
Baricitinib	Other	Inhibitor of JAK1/2	Nova Scotia Health Authority	O	EUA
Tocilizumab	Antibody	IL-6R	Roche	O	EUA
Casirivimab/Imdevimab (REGN-COV2)	Antibody	RBD of SARS-CoV-2 spike glycoprotein	Regeneron Pharmaceuticals		EUA[b]
Bamlanivimab (LY-CoV555)	Antibody	Spike glycoprotein of SARS-CoV-2	Eli Lilly		EUA[b]
Etesevimab (LY-CoV016)	Antibody	Spike glycoprotein of SARS-CoV-2	Eli Lilly		EUA[b]
Regdanvimab (CT-P59)	Antibody	RBD of SARS-CoV-2 spike glycoprotein	Celltrion		Approved in EU, Korea
Sotrovimab (VIR-7831)	Antibody	Spike glycoprotein of SARS-CoV-2	GlaxoSmithKline		EUA
Tixagevimab/Cilgavimab (Evusheld, AZD7442)	Antibody	RBD of SARS-CoV-2 spike glycoprotein	AstraZeneca		EUA
Bebtelovimab (LY-CoV1404)	Antibody	Spike glycoprotein of SARS-CoV-2	Eli Lilly		EUA

FDA: Food and Drug Administration, RBD: receptor-binding domain, EUA: emergency use authorization.
[a]The FDA has revoked the emergency use authorization of this drug for the treatment of SARS-CoV-2 because of side effects observed in clinical trials (June 15, 2020).
[b]These drugs are not currently authorized for use against the omicron variant.

Imdevimab (Regeneron Pharmaceuticals), Sotrovimab (GlaxoSmithKline), Evusheld (AstraZeneca), Bamlanivimab (Eli Lilly), Etesevimab (Eli Lilly), and Bebtelovimab (Eli Lilly) (Table 2).

Chloroquine was previously approved by the FDA for pan-virus infections and was urgently approved for SCoV2 under EUA in the early stages of the pandemic. However, the FDA has revoked its emergency authorization because side effects were observed in clinical trials (June 15, 2020) [27]. Casirivimab/Imdevimab, Bamlanivimab, and Etesevimab, which received EUA, are not currently authorized because their effectiveness has not been guaranteed for the omicron variant [27]. Prescription of these antibodies for SCoV2 has been suspended until further notice from the FDA.

Regdanvimab (Celltrion), another antibody against the spike glycoprotein of SCoV2, is officially approved in Europe and South Korea [29].

4. Conclusion

Currently, the COVID-19 pandemic is being countered through the efforts and sacrifices of medical staff worldwide, along with urgently approved vaccines and therapeutics. To completely overcome the pandemic, researchers are developing hundreds of vaccines and therapeutic candidates, as reviewed above. Although the global death toll has continued to decrease since February 2022 to less than 10,000 cases per week now, more than 3 million cases per week have unfortunately continued to occur since May 2022, mainly in Europe and the Americas [4]. The development of vaccines and therapeutics that respond to viral mutagenesis needs to be accelerated for achieving an endemic state.

Since humans have been exhausted mentally and economically because of accumulated damage for three years, the emergence of a fatal mutant of SCoV2 may cause unaffordable damage when the second wave of the pandemic comes. In addition, owing to global climate and environmental changes, new, fatal viruses are expected to spread in the near future, such as MERS, influenza, Ebola virus, Nipah virus, and Monkeypox virus, in addition to SCoV3. In this respect, experiencing commercialization of next-generation technologies, such as mRNA platform

vaccines and nucleotide mimics, is a great achievement in this pandemic. Preparation for the next pandemic situation should be initiated on the basis of these strategies.

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grants (NRF-2021M3E5E 3080540 and NRF-2020M3A9I2108176 to S.J.K.), the NRF grant funded by the Korea government (MSIT) (NRF-2020R1C1C1010106 to W.L.), and the National Research Council of Science & Technology (NST) grant (CRC-16-01-KRICT to S.J.K.) funded by the Korea government (MSIP).

Ethical Statements

The authors declare no conflicts of interest.
Ethical approval and informed consent were not required for the study.

Electronic Supplementary Material (ESM)

The online version of this article (doi: 10.1007/s12257-022-0188-4) contains supplementary material, which is available to authorized users.

References

1. Delorey, T. M., C. G. K. Ziegler, G. Heimberg, R. Normand, Y. Yang, Å. Segerstolpe, D. Abbondanza, S. J. Fleming, A. Subramanian, D. T. Montoro, K. A. Jagadeesh, K. K. Dey, P. Sen, M. Slyper, Y. H. Pita-Juárez, D. Phillips, J. Biermann, Z. Bloom-Ackermann, N. Barkas, A. Ganna, J. Gomez, J. C. Melms, I. Katsyv, E. Normandin, P. Naderi, Y. V. Popov, S. S. Raju, S. Niezen, L. T. Tsai, K. J. Siddle, M. Sud, V. M. Tran, S. K. Vellarikkal, Y. Wang, L. Amir-Zilberstein, D. S. Atri, J. Beechem, O. R. Brook, J. Chen, P. Divakar, P. Dorceus, J. M. Engreitz, A. Essene, D. M. Fitzgerald, R. Fropf, S. Gazal, J. Gould, J. Grzyb, T. Harvey, J. Hecht, T. Hether, J. Jané-Valbuena, M. Leney-Greene, H. Ma, C. McCabe, D. E. McLoughlin, E. M. Miller, C. Muus, M. Niemi, R. Padera, L. Pan, D. Pant, C. Pe'er, J. Pfiffner-Borges, C. J. Pinto, J. Plaisted, J. Reeves, M. Ross, M. Rudy, E. H. Rueckert, M. Siciliano, A. Sturm, E. Todres, A. Waghray, S. Warren, S. Zhang, D. R. Zollinger, L. Cosimi, R. M. Gupta, N. Hacohen, H. Hibshoosh, W. Hide, A. L. Price, J. Rajagopal, P. R. Tata, S. Riedel, G. Szabo, T. L. Tickle, P. T. Ellinor, D. Hung, P. C. Sabeti, R. Novak, R. Rogers, D. E. Ingber, Z. G. Jiang, D. Juric, M. Babadi, S. L. Farhi, B. Izar, J. R. Stone, I. S. Vlachos, I. H. Solomon, O. Ashenberg, C. B. M. Porter, B. Li, A. K. Shalek, A. C. Villani, O. Rozenblatt-Rosen, and A. Regev (2021) COVID-19 tissue atlases reveal SARS-CoV-2 pathology and cellular targets. *Nature.* 595: 107-113.
2. Odilov, A., A. Volkov, A. Abdullaev, T. Gasanova, T. Lipina, and I. Babichenko (2021) COVID-19: multiorgan dissemination of SARS-CoV-2 is driven by pulmonary factors. *Viruses*. 14: 39.
3. Ahn, D. G., H. J. Shin, M. H. Kim, S. Lee, H. S. Kim, J. Myoung, B. T. Kim, and S. J. Kim (2020) Current status of epidemiology, diagnosis, therapeutics, and vaccines for novel coronavirus disease 2019 (COVID-19). *J. Microbiol. Biotechnol.* 30: 313-324.
4. WHO COVID-19 Dashboard. https://covid19.who.int/.
5. Zhou, H., J. Yang, C. Zhou, B. Chen, H. Fang, S. Chen, X. Zhang, L. Wang, and L. Zhang (2021) A review of SARS-CoV2: compared with SARS-CoV and MERS-CoV. *Front. Med. (Lausanne)* 8: 628370.
6. Abdelghany, T. M., M. Ganash, M. M. Bakri, H. Qanash, A. M. H. Al-Rajhi, and N. I. Elhussieny (2021) SARS-CoV-2, the other face to SARS-CoV and MERS-CoV: future predictions. *Biomed. J.* 44: 86-93.
7. World Health Organization, R&D Blue Print; COVID-19 vaccine tracker and landscape. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.
8. Mattoo, S. S. and J. Myoung (2021) A promising vaccination strategy against COVID-19 on the horizon: heterologous immunization. *J. Microbiol. Biotechnol.* 31: 1601-1614.
9. VIPER Group COVID19 Vaccine Tracker Team, COVID-19 vaccine development and approvals tracker. https://covid19.trackvaccines.org/.
10. Chinese Clinical Trial Registry, A phase III clinical trial of influenza virus vector COVID-19 vaccine for intranasal spray (DelNS1-2019-nCoV-RBD-OPT1). http://www.chictr.org.cn/showprojen.aspx?proj=133897.
11. Pan African Clinical Trials Registry, A phase III clinical trial of influenza virus vector COVID-19 vaccine for intranasal spray (DelNS1-2019-nCoV-RBD-OPT1). https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=17163.
12. Korea Biomedical Review, Genexine to give up Covid-19 vaccine development. http://www.koreabiomed.com/news/articleView.html?idxno=13283.
13. ClinicalTrials.gov, A study to evaluate the immunogenicity and safety of omicron variant vaccines in comparison with mRNA-1273 booster vaccine for COVID-19. https://clinicaltrials.gov/ct2/show/NCT05249829.
14. ClinicalTrials.gov, A study to evaluate the immunogenicity and safety of mRNA vaccine boosters for SARS-CoV-2 (COVID-19) variants. https://clinicaltrials.gov/ct2/show/NCT04927065.
15. Choi, A., M. Koch, K. Wu, L. Chu, L. Ma, A. Hill, N. Nunna, W. Huang, J. Oestreicher, T. Colpitts, H. Bennett, H. Legault, Y. Paila, B. Nestorova, B. Ding, D. Montefiori, R. Pajon, J. M. Miller, B. Leav, A. Carfi, R. McPhee, and D. K. Edwards (2021) Safety and immunogenicity of SARS-CoV-2 variant mRNA vaccine boosters in healthy adults: an interim analysis. *Nat. Med.* 27: 2025-2031.
16. Ying, B., S. M. Scheaffer, B. Whitener, C. Y. Liang, O. Dmytrenko, S. Mackin, K. Wu, D. Lee, L. E. Avena, Z. Chong, J. B. Case, L. Ma, T. T. M. Kim, C. E. Sein, A. Woods, D. M. Berrueta, G. Y. Chang, G. Stewart-Jones, I. Renzi, Y. T. Lai, A. Malinowski, A. Carfi, S. M. Elbashir, D. K. Edwards, L. B. Thackray, and M. S. Diamond (2022) Boosting with variant-matched or historical mRNA vaccines protects against Omicron infection in mice. *Cell.* 185: 1572-1587.e11.
17. ClinicalTrials.gov, A study to evaluate the immunogenicity and safety of mRNA-1283 COVID-19 vaccine boosters. https://clinicaltrials.gov/ct2/show/NCT05137236.
18. Moderna, Moderna reports second quarter fiscal year 2021 financial results and provides business updates. https://investors.modernatx.com/news/news-details/2021/Moderna-Reports-Second-Quarter-Fiscal-Year-2021-Financial-Results-and-Provides-Business-Updates-08-05-2021/default.aspx.

19. CureVac, CureVac to shift focus of COVID-19 vaccine development to second-generation mRNA technology. https://www.curevac.com/en/curevac-to-shift-focus-of-covid-19-vaccine-development-to-second-generation-mrna-technology/.
20. Sanofi, Sanofi to focus its COVID-19 development efforts on the recombinant vaccine candidate. https://www.sanofi.com/en/media-room/press-releases/2021/2021-09-28-18-44-47-2304800.
21. ClinicalTrials.gov, A heterologous prime-boost study to evaluate immunogenicity and safety of mRNA-1273 with MVC-COV1901 in adults. https://clinicaltrials.gov/ct2/show/NCT05079633.
22. ClinicalTrials.gov, A heterologous 3rd COVID-19 vaccine of MVC-COV1901 to evaluate immunogenicity and safety in adults with ChAdOx1-nCov-19. https://clinicaltrials.gov/ct2/show/NCT05097053.
23. ClinicalTrials.gov, Phase 3 booster study for the SARS-CoV-2 rS vaccines. https://clinicaltrials.gov/ct2/show/NCT05372588.
24. ClinicalTrials.gov, Evaluation of the safety and immunogenicity of SII vaccine constructs based on the SARS-CoV-2 (COVID-19) variant in adults. https://clinicaltrials.gov/ct2/show/NCT05029856.
25. Government of Canada, Authorized vaccines; Medicago Covifenz COVID-19 vaccine. https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/vaccines/medicago.html#shr-pg0.
26. BioRender, COVID-19 vaccine & therapeutics tracker. https://biorender.com/covid-vaccine-tracker/.
27. U.S. Food and Drug Administration, Coronavirus disease 2019 emergency use authorization information. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.
28. Rothenberger, S., D. L. Hurdiss, M. Walser, F. Malvezzi, J. Mayor, S. Ryter, H. Moreno, N. Liechti, A. Bosshart, C. Iss, V. Calabro, A. Cornelius, T. Hospodarsch, A. Neculcea, T. Looser, A. Schlegel, S. Fontaine, D. Villemagne, M. Paladino, Y. Kaufmann, D. Schaible, I. Schlegel, D. Schiegg, C. Zitt, G. Sigrist, M. Straumann, F. Sacarcelik, J. Wolter, M. Comby, J. M. Adler, K. Eschke, M. Nascimento, A. Abdelgawad, A. D. Gruber, J. Bushe, O. Kershaw, H. Lyoo, C. Wang, W. Li, I. Drulyte, W. Du, H. K. Binz, R. Herrup, S. Lusvarghi, S. N. Neerukonda, R. Vassell, W. Wang, S. Mangold, C. Reichen, F. Radom, C. G. Knutson, K. K. Balavenkatraman, K. Ramanathan, S. Lewis, R. Watson, M. A. Haeuptle, A. Zürcher, K. M. Dawson, D. Steiner, C. D. Weiss, P. Amstutz, F. J. M. van Kuppeveld, M. T. Stumpp, B.-J. Bosch, O. Engler, and J. Trimpert (2022) Ensovibep, a novel trispecific DARPin candidate that protects against SARS-CoV-2 variants. *bioRxiv*. 2021.02.03.429164.
29. European Medicines Agency, Medicine authorisation for treating COVID-19; Regkirona (regdanvimab). https://www.ema.europa.eu/en/medicines/human/EPAR/regkirona.