JKMS

Review Article
Infectious Diseases, Microbiology & Parasitology

Check for updates

COVID-19 Vaccination in Korea: Past, Present, and the Way Forward

Eliel Nham [ID],[1,2] Joon Young Song [ID],[1,2] Ji Yun Noh [ID],[1,2] Hee Jin Cheong [ID],[1,2] and Woo Joo Kim [ID] [1,2]

[1]Division of Infectious diseases, Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea
[2]Vaccine Innovation Center-KU Medicine (VIC-K), Seoul, Korea

OPEN ACCESS

Address for Correspondence:
Joon Young Song, MD, PhD
Division of Infectious diseases, Department of Medicine, Korea University Guro Hospital, Korea University College of Medicine, 148 Gurodong-ro, Guro-gu, Seoul 08308, Korea.
Email: infection@korea.ac.kr

ORCID iDs
Eliel Nham [ID]
https://orcid.org/0000-0001-7509-4863
Joon Young Song [ID]
https://orcid.org/0000-0002-0148-7194
Ji Yun Noh [ID]
https://orcid.org/0000-0001-8541-5704
Hee Jin Cheong [ID]
https://orcid.org/0000-0002-2532-1463
Woo Joo Kim [ID]
https://orcid.org/0000-0002-4546-3880

ABSTRACT

Since its first emergence in late 2019, severe acute respiratory syndrome coronavirus-2 has claimed more than 6.5 million lives worldwide and continues to infect hundreds of thousands of people daily. To combat this once-in-a-century disaster, several vaccines have been developed at unprecedented speeds. Novel vaccine platforms (messenger ribonucleic acid vaccines and adenoviral vector vaccines) have played a major role in the current pandemic. In Korea, six vaccines, including a domestically developed recombinant vaccine, have been approved. As in other countries, vaccines have been proven to be safe and highly effective in Korea. However, rare serious adverse events and breakthrough infections have undermined public trust in the vaccines, even while the benefits of vaccination far outweigh the risks. The rise of the omicron variant and the subsequent increase in excess mortality demonstrated that while vaccines are a key component of the pandemic response, it alone can fail without non-pharmaceutical interventions like masking and social distancing. The pandemic of coronavirus disease has revealed both the strengths and weaknesses of our healthcare system and pandemic preparedness. When the next pandemic arrives, improved risk communication and vaccine development should be prioritized. To enable timely vaccine development, it is essential to make strategic and sufficient investments in vaccine research and development.

Keywords: COVID-19; SARS-CoV-2; Vaccination; Vaccine Efficacy; Safety

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged in late 2019 in patients presenting with pneumonia of unknown etiology, which was later named coronavirus disease 2019 (COVID-19). Soon after its discovery, the first case of COVID-19 in South Korea was confirmed in January 20, 2020.[1] In less than 100 days, the World Health Organization (WHO) declared the COVID-19 pandemic.[2] As of September 27, 2022, this zoonotic virus has infected more than 616 million people and claimed more than 6.5 million lives worldwide, both figures likely being vastly underestimated.[3] People over 60 and people with chronic medical conditions are disproportionally affected by severe infections.[4-8]

Author Contributions

Conceptualization: Nham E, Song JY. Data curation: Nham E. Formal analysis: Nham E, Song JY. Investigation: Nham E, Song JY, Noh JY, Cheong HJ, Kim WJ. Methodology: Nham E, Song JY, Noh JY, Cheong HJ, Kim WJ. Validation: Nham E, Song JY. Visualization: Nham E, Song JY. Writing - original draft: Nham E, Song JY. Writing - review & editing: Nham E, Song JY, Noh JY, Cheong HJ, Kim WJ.

To mitigate the pandemic, interpersonal pathogen transmission must be halted by weakening viral replication. This is particularly challenging in the case of SARS-CoV-2 since asymptomatic persons, who constitute a considerable proportion of those infected, can still spread the virus. Universal masking and social distancing, especially the latter, are not sustainable because of long-term public fatigue. Antiviral drugs were unavailable at an early stage of the pandemic and would only become useful after infection. Therefore, safe and effective vaccines are the best measures to limit viral transmission.

The rapid development of highly effective and safe vaccines has exemplified the power of science during the COVID-19 pandemic. Notwithstanding, the pandemic also revealed darker aspects of modern society, such as the politicization of the pandemic response, health inequities, vaccine nationalism, and widespread misinformation. As a result, severe infections and deaths continue to occur, even with the availability of effective vaccines. Lingering disabling symptoms, collectively known as "long COVID," also significantly compound the social burdens.[9,10]

Here, we review vaccine technologies that have been widely adopted during the current pandemic, as well as studies on COVID-19 vaccination in Korea. We also describe how mass vaccination has unfolded thus far and how we may respond to this pandemic in the future.

COVID-19 VACCINE PLATFORMS

Six COVID-19 vaccines have been authorized in Korea, including two messenger ribonucleic acid (mRNA) vaccines, two adenoviral vector vaccines, and two recombinant nanoparticle vaccines. ChAdOx1 nCoV-19 (Covishield™, Oxford-AstraZeneca) was first authorized on February 10, 2021, followed by BNT162b2 (Comirnaty™, Pfizer-BioNTech; March 5, 2021), Ad26.COV2.S (Jcovden™, Janssen; April 7, 2021), mRNA-1273 (Spikevax™, Moderna; May 21, 2021), NVX-CoV2373 (Nuvaxoid™, Novavax; January 12, 2022), and GBP510 (SKYCovione™, SK Bioscience; June 29, 2022) (**Table 1**). As of September 25, 2022, 128,710,064 doses of COVID-19 vaccines were administered: BNT162b2 (62.9%), mRNA-1273 (19.5%), ChAdOx1 (15.8%), Ad26.COV2.S (1.2%), NVX-CoV2373 (0.6%) and GBP510 (< 0.1%).[11] The characteristics of each vaccine platform are summarized in **Table 2**.

mRNA vaccines were first commercialized during the COVID-19 pandemic. They contain mRNA encoding the peptide sequence of the SARS-CoV-2 spike protein (the main antigen)

Table 1. Six coronavirus disease 2019 vaccines that have been authorized in Korea

Vaccines	Date of authorization	Doses imported/manufactured[a]	Approved age, yr
ChAdOx1 nCoV-19 (Covishield™, Oxford-AstraZeneca)	February 10, 2021	20,005,000	≥ 18
BNT162b2 (Comirnaty™, Pfizer-BioNTech)	March 5, 2021	81,904,000 (monovalent) 1,329,030 (0.1 mg/mL for children aged 5–11) 8,908,000 (bivalent)	≥ 5
Ad26.COV2.S (Jcovden™, Janssen)	April 7, 2021	1,999,000	≥ 18
mRNA-1273 (Spikevax™, Moderna)	May 21, 2021	34,478,000 (monovalent) 11,733,000 (bivalent)	≥ 18
NVX-CoV2373 (Nuvaxoid™, Novavax)	January 12, 2022	2,932,000	≥ 18
GBP510 (SKYCovione™, SK Bioscience)	June 29, 2022	609,000	≥ 18

[a]Reported by Ministry of Food and Drug Safety, as of November 14, 2022.[110]

Table 2. Overview of the coronavirus disease 2019 vaccine platform

Characteristics	Messenger RNA vaccines	Adenoviral vector vaccines	Recombinant nanoparticle vaccines
Advantages	- High efficacy and effectiveness - Rapid design - Scalability	- Good cellular immune response - Scalability - Low cost	- Favorable safety profile - Minimal cold chain dependence (easy storage and distribution) - Worldwide manufacturing capacity
Disadvantages	- High cold-chain dependence (need for deep freezer) - Multi-dose vials requiring multiple persons to be vaccinated - High reactogenicity	- Immune interference by immunity to adenoviral vectors - High reactogenicity - Higher incidence of inflammatory disorders involving various organs than other platforms	- Need for adjuvants - Slow developmental process - High cost
Efficacy (Primary series only)	- Laboratory-confirmed infections: BNT162b2[a] 95% (95% CI, 90.3–97.6) mRNA-1273[b] 94.1% (95% CI, 89.3–96.8) - Severe infections: BNT162b2[c] 88.9 (95% CI, 20.1–99.7) mRNA-1273 100%	- Laboratory-confirmed infections: ChAdOx1 nCoV-19 62.1% (95% CI, 41.0–75.7)[d] 90.0% (95% CI, 67.4–97.0)[e] 74.0% (95% CI, 65.3–80.5)[f] Ad26.COV2.S 66.9% (95% CI, 59.1–73.4) - Severe infections: ChAdOx1 nCoV-19 100% Ad26.COV2.S 85.4% (95% CI, 54.2–96.9)	- Laboratory-confirmed infections: NVX-CoV2373 89.7% (95% CI, 80.2–94.6)[g] 90.4% (95% CI, 82.9–94.6)[h] GBP510 Not available - Severe infections: NVX-CoV2373 100%[g] 100% (95% CI, 87.0–100)[h] GBP510 Not available
Major serious adverse events	- Myocarditis/pericarditis	- Thrombotic thrombocytopenia - Neuroinflammatory diseases (e.g., Guillain-Barre syndrome, transverse myelitis)	- So far, no adverse event concerns specific to this platform

CI = confidence interval.

[a]Cases were counted from seven days after the second dose; [b]Cases were counted from 14 days after the second dose; [c]All who received at least one dose were included in the analysis; [d]Efficacy in those who were primed by standard dose; [e]Efficacy in those who were primed by half dose; [f]Efficacy in the American trial[111]; [g]Efficacy in the UK trial[29]; [h]Efficacy in the American trial.[28]

which is packed in lipid nanoparticles and delivered into cells, where it is translated as a whole or a specific portion of the antigen. mRNA vaccines have gained popularity because of their high efficacy and rapid production potential (**Table 1**).[12] Their efficacy is the highest among the available COVID-19 vaccines, with 94–95% protection against laboratory-confirmed infections.[13,14] Moreover, the mRNA cannot integrate into the human genome because it does not enter the cell nucleus, averting concerns of acquired genetic diseases such as cancer and autoimmune diseases. On the other hand, mRNA vaccines have notable limitations such as restrictive storage conditions (notably in deep freeze due to mRNA instability) and multi-dose vial formulation.[15] A noteworthy adverse event (AE) of mRNA vaccines against COVID-19 is myocarditis/pericarditis. COVID-19 mRNA vaccine-related myocarditis may be caused by autoimmunity (through mimicry between the spike protein and cardiac self-antigens) and hypersensitivity reactions.[16,17] Although the vast majority of myocarditis/pericarditis cases were mild, they contribute to vaccine hesitancy among young people.[18]

Adenoviral vector vaccines are not entirely new; based on this platform, an authorized vaccine against the Ebola virus disease (Ad26.ZEBOV and MVA-BN-Filo) had already been administered to over 20,000 individuals by April 2020.[19,20] However, due to the rarity of the Ebola virus disease outside of endemic regions, it was largely an unknown form of vaccine. An adenovirus vector is a replication-incompetent adenovirus that carries the genetic sequence of an antigen within its gene. When injected into the body, the vector enters the cell and releases its genome inside the nucleus. The genetic sequence is transcribed and translated to produce the antigen. Adenoviral vector vaccines have a notable advantage of inducing strong cellular immune responses.[21] In addition, adenoviral vector vaccines are more stable than mRNA vaccines, forgoing the need for storage in extremely cold temperatures. They are

not mutagenic because the DNA within the adenoviral vector is modified so that it does not integrate into the human genome. However, pre-existing immunity against vectors may reduce their immunogenicity.[22] Despite the use of adenoviruses with low human seroprevalence (such as the chimpanzee adenovirus or human adenovirus type 26), adenoviral vector vaccines are generally less immunogenic and less effective compared to the mRNA vaccines.[23-25] In the ChAdOx1 nCoV-19 and Ad26.COV2.S trials, vaccine efficacy was in the range of 60–90%. In addition, there are concerns of rare but serious AEs, including vaccine-induced thrombosis with thrombocytopenia (VITT, approximately 10 per million doses) and Guillain-Barre syndrome (GBS, approximately 1 per million doses). While, after receiving an mRNA vaccine, only a small fraction of myocarditis/pericarditis cases were critical, VITT cases experienced a much higher fatality (22%) in a national cohort.[18,26]

Recombinant nanoparticle vaccines could contribute to alleviating vaccine inequity with its scalable production and minimal cold chain dependence. Although they are classified as protein subunit vaccines, they differ in that the protein molecules are embedded in nanoparticles. These nanoparticle scaffolds enhance immunogenicity and protect protein molecules from proteases in the blood. A key strength of these vaccines is their favorable safety profile, as experienced in various kinds of infectious disease vaccines.[27] However, protein subunit vaccines have a weakness to induce insufficient immune response, which can be strengthened by the addition of an adjuvant. Recombinant nanoparticle vaccines against COVID-19 were available later due to a slower developmental process than the other vaccines mentioned above, which is another weakness of protein-based vaccines. Two recombinant nanoparticle vaccines are available with domestic approval: NVX-CoV2373 and GBP510. NVX-CoV2373 is composed of stabilized and full-length recombinant SARS-CoV-2 spike protein trimers, which are assembled into nanoparticles and adjuvanted with Matrix-M.[28] In the United Kingdom (UK) and the United States (US), NVX-CoV2373 was approximately 90% effective against laboratory-confirmed infections.[28,29] GBP510 is a self-assembling, two-component nanoparticle that is adjuvanted with AS03. The nanoparticle displays multiple conformational and conserved neutralizing epitopes of the SARS-CoV-2 receptor-binding domain. GBP510 was approved by a non-inferiority trial compared to ChAdOx1 nCoV-19, the first authorized vaccine in Korea. In the phase 3 clinical trial, the geometric mean titer ratio of the neutralizing antibody (NAb) was 2.93 (GBP 510 vs. ChAdOx1 nCoV-19) after two-dose primary series vaccination, satisfying the superior immunogenicity criteria.[30]

STUDIES ON THE IMMUNOGENICITY OF COVID-19 VACCINES IN KOREA

There are several studies on the immunogenicity of the primary vaccination series in Korean adults.[31-34] In all but one of the studies on the Ad26.COV2.S vaccine cohort, BNT162b2 was given three weeks apart and ChAdOx1 nCoV-19 was given 12 weeks apart. Participants who received BNT162b2 sustained higher NAb levels throughout the study period than ChAdOx1 nCoV-19 recipients. In all studies, antibody levels waned several months after the completion of the primary series, and the decline was faster in older participants.

A considerable number of healthcare workers (HCWs) received heterologous primary series vaccination (with ChAdOx1 nCoV-19 as the first dose and an mRNA vaccine as the second dose) because of the introduction of age restriction for receiving ChAdOx1 nCoV-19 due to concerns of VITT. Bae et al. recruited 199 HCWs who received 2 doses of ChAdOx1 nCoV-19

12 weeks apart (ChAd-ChAd group), 200 HCWs who received 2 doses of BNT162b2 3 weeks apart (BNT-BNT group), and 100 HCWs who received ChAdOx1 nCoV-19 as the first dose and BNT162b2 as the second dose 12 weeks apart (ChAd-BNT group). The study measured NAb levels using the plaque reduction neutralization test.[35] The 50% neutralization dose of the BNT-BNT group (2,119, 95% confidence interval [CI], 1,756–2,556) and the ChAd-BNT group (2,367, 95% CI, 1,970–2,846) were similar, while also being significantly higher than that of the ChAd-ChAd group (392, 95% CI, 326–471). Non-Korean studies also reported that heterologous vaccination, with an adenoviral vector vaccine and an mRNA vaccine, was just as immunogenic as homologous vaccination with an mRNA vaccine. In terms of immunogenicity, it was also superior to homologous vaccination with an adenoviral vector vaccine, without significant differences in the AE profile.[23,36]

Two studies on the immunogenicity of a fourth dose were identified.[37,38] In one, the National Institute of Infectious Diseases of Korea obtained blood samples 4 weeks apart from 74 residents in 2 long-term care facilities, in order to measure NAb levels.[38] The NAb titer was 2–2.5 times higher at 2 weeks after the fourth vaccination than at 4 months after the third vaccination. There was another 6.4-to 7.4-fold increase in NAb titers at 4 weeks compared to 2 weeks after the fourth dose.

Hybrid immunity by natural SARS-CoV-2 infection and vaccination was also studied.[39-41] In a study by Noh et al.,[41] a robust NAb immune response was induced even with a single-dose of COVID-19 vaccination, when vaccinated at long intervals (more than 12 months) after SARS-CoV-2 infection. However, remarkable ceiling effects were observed with repeated vaccinations. In a study by Kang et al.,[39] similar NAb titers were induced between uninfected individuals who received two-dose mRNA vaccines and prior-infected individuals who received single-dose mRNA vaccine. Among prior-infected individuals, Nab titers were significantly higher in vaccine recipients at around 18 months compared to those vaccinated within six months after SARS-CoV-2 infection. Consistent with the study by Noh et al.,[41] vaccinating twice after SARS-CoV-2 infection did not raise NAb titers further. In prior-infected individuals, Choi et al.[40] reported higher NAb levels and a broader neutralization spectrum induced by a fourth vaccination with NVX-CoV2373, compared to those in uninfected counterparts. Although limited by small sample sizes, these findings are consistent with non-Korean studies and suggest important considerations in establishing vaccination policies for people who had COVID-19.[42,43]

REAL-WORLD EFFECTIVENESS OF COVID-19 VACCINES IN KOREA

Two studies on primary series vaccine effectiveness (VE) in adults were identified (**Fig. 1**, **Table 3**).[44,45] In one, the incidence of laboratory-confirmed SARS-CoV-2 infection of any severity and severe infection was compared between unvaccinated people and those vaccinated at least once from March 13, 2021, to October 21, 2021.[44] Among unvaccinated individuals, the age-adjusted incidence of infection of any severity (5.69 per 100,000 person-days) was 1.9 times higher than that among partially vaccinated individuals (3.05 per 100,000 person-days) and 2.7 times higher than that among fully vaccinated individuals (2.13 per 100,000 person-days). This translated into an overall VE of 63%. The age-adjusted incidence of severe infection in unvaccinated individuals was 0.16 per 100,000 person-days, compared to 0.02 per 100,000 person-days in people vaccinated at least once, resulting in a VE of 93%.
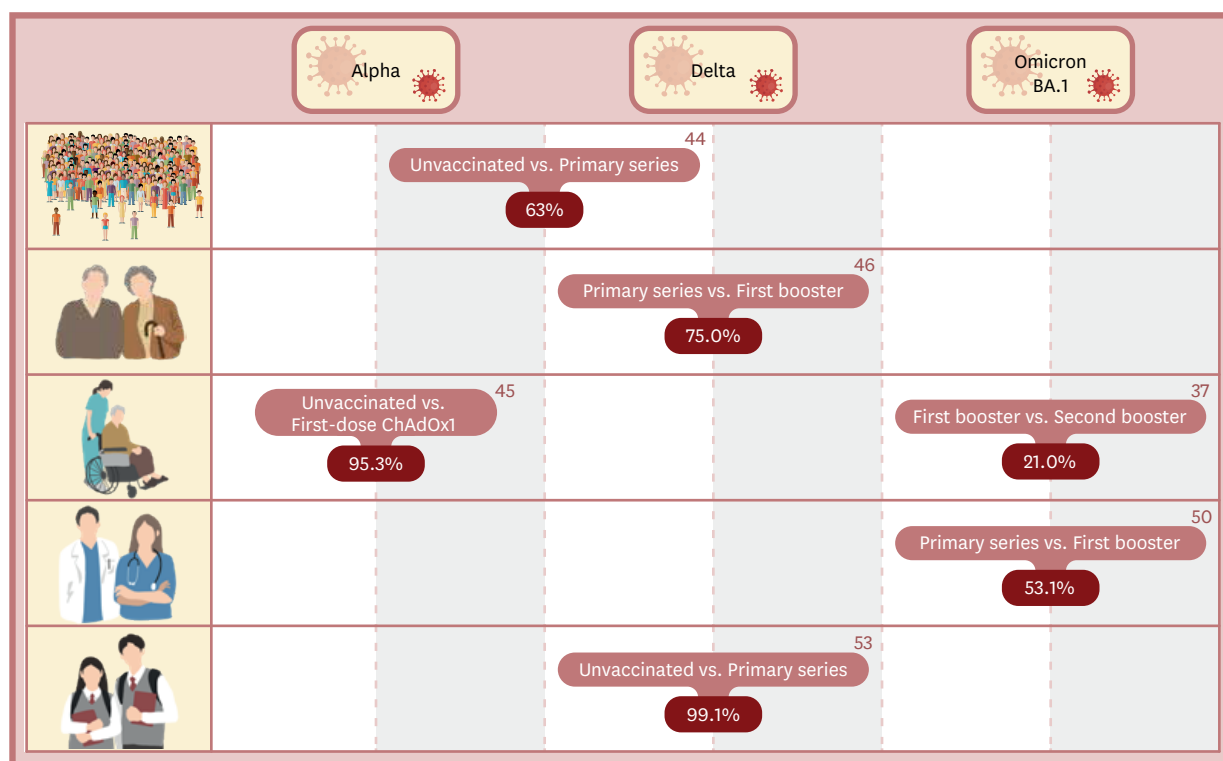
Fig. 1. Vaccine effectiveness against laboratory-confirmed coronavirus disease 2019 across severe acute respiratory syndrome coronavirus 2 variants and study population. The numbers displayed at the top right of each item in superscript refer to the citation number.

Table 3. Summary of studies on coronavirus disease 2019 vaccine effectiveness in Korea

Studies	Study period	Predominant viral strain	Study population	Comparators	Vaccine effectiveness (95% CI)	Reference
Yi et al.	Mar 2021–Oct 2021	Alpha, delta	General population	Unvaccinated vs. primary series	Laboratory-confirmed infection: 63%[a] Severe infection: 93%[a] Death: 95%[a]	[44]
Kim et al.	May 2021	Alpha	LTCF residents, staff and caregivers	Unvaccinated vs. first-dose ChAdOx1 nCoV-19	Laboratory-confirmed infection: 95.3% (67.7–99.3%)	[45]
Kim et al.	Oct 2021–Jan 2022	Delta	General population aged 60+	Primary series vs. first booster (third dose)	Symptomatic infection: 75.0% (74.1–75.8%) Severe infection: 91.6% (89.2–93.4%)	[46]
Park et al.	Feb 2022–Apr 2022	Omicron (BA.1)	LTCF residents and staff	Unvaccinated vs. first booster (third dose)	Severe infection: 71% (36–87%) Death: 65% (21–85%)	[47]
Kim et al.	Feb 2022–Apr 2022	Omicron (BA.1)	Healthcare workers	Primary series vs. first booster	Laboratory-confirmed infection: 53.1% (13–75%)	[50]
Kim et al.	Feb 2022–May 2022	Omicron (BA.1)	Immunocompromised persons, LTCF residents	First booster vs. second booster	Laboratory-confirmed infection: 21.0% (20.1–21.8%) Severe infection: 50.5% (44.0–56.3%) Death: 54.1% (47.3–60.0%)	[37]
Choe et al.	Jul 2021–Aug 2021	Delta	18-year-old	Unvaccinated vs. primary series	Laboratory-confirmed infection: 99.1% (98.5–99.5%)	[53]

CI = confidence interval, LTCF = long-term care facility.
[a]95% CI not reported.

There are some VE studies on booster doses as well. The Korean Disease Control and Prevention Agency (KDCA) collected data from 10,999,292 Koreans aged 60 years or older and compared the rates of symptomatic SARS-CoV-2 infection, severe infection, and mortality between individuals who received only 2-doses of COVID-19 vaccine and those who received 3-doses.[46] The study period was from October 2021 to January 2022, during

which the delta variant (B.1.617.2) was predominant. The adjusted VE of a third dose was 75.0% (95% CI, 74.1–75.8%) for symptomatic infections, 91.6% (95% CI, 89.2–93.4%) for severe infections, and 92.3% (95% CI, 88.7–94.8%) for death. The KDCA also investigated VE in 2,241 patients and HCWs in 5 long-term care facilities from February 6, 2022, to April 2, 2022, when the omicron variant (BA.1) was predominant.[47] People over 60 years old accounted for 67.6% and those over 75 years accounted for 38.3%. Compared to unvaccinated individuals, those who received only 2-doses had a VE of 54% (95% CI, −19 to 82%) for severe COVID-19 and 53% (95% CI, −29 to 83%) for death, adjusted for age, sex, and antiviral drug use. The adjusted VE was higher in people who received booster doses (a third dose): 71% (95% CI, 36–87%) for severe COVID-19 and 65% (95% CI, 21–85%) for death. Although the studies were not directly comparable due to differences in the study population, vaccine administration, and study design, the findings summarized above nonetheless support the conclusions of non-Korean studies.[48,49] In a retrospective single-center study, Kim et al.[50] compared primary series vaccinations (2 doses) and booster vaccinations (a third dose) in terms of prevention of laboratory-confirmed SARS-CoV-2 infection in February 2022. The adjusted VE of the third vaccination was 53.1% (95% CI, 13–75%). However, when the time elapsed after vaccination was included in the multivariable analysis, the statistical significance of VE disappeared (29%; 95% CI, −50 to 66%), suggesting that the time since the last vaccination may be more important than having the third dose itself.

Additionally, KDCA investigated the VE of a fourth dose in immunocompromised people and residents of long-term care facilities.[37] From February 16, 2022, to April 30, 2022, a total of 1,509,970 individuals who received a third dose more than 4 months ago were included. Fourteen days after vaccination, the VE of the fourth dose was 21.0% against laboratory-confirmed infection, 50.5% against severe COVID-19, and 54.1% against death. Thirty days after the fourth dose, the VE against infection decreased to 8.9%. While there was a remarkable increase in NAb levels 4 weeks after the fourth dose in the previous study, this might have been inadequate to protect against the omicron variant.[38] Canadian and Swedish studies on fourth doses in high-risk individuals reported similar values.[51,52]

To date, only one large-scale VE study is available in the pediatric population because of the low vaccine uptake rate, especially in younger children.[53] In 2021, high school students (aged 18 years old) were required to be vaccinated before the national college entrance exam. Of 454,876 students, 95.4% completed the primary series. Choe et al. combined COVID-19 case reports from the Ministry of Education and data from the national immunization registry to estimate the VE among students. They found that the VE against laboratory-confirmed SARS-CoV-2 infection was 99.1% (95% CI, 98.5–99.5%) at 14 days after the first dose vaccination.

VACCINE EFFECTIVENESS AGAINST THE OMICRON BA.4/5 SUBVARIANTS

Since the omicron has become the dominant variant, it has not been replaced by an entirely new variant as before, but rather by its own subvariants. As of November, 2022, BA.4 and BA.5 (collectively called BA.4/5) are the most frequently encountered variants in Korea. These variants can evade immunity more effectively than BA.1/2, which are earlier subvariants which already had significant immune-evading capabilities.[54] Up until mid-November, 2022, there has been no Korean study on the VE against omicron BA.4/5, and it has to be extrapolated from non-Korean studies. The largest study (n = 123,236) analyzed the VE of

3- and 4-doses of mRNA-1273 against BA.4/5-related hospitalization using the US Kaiser Permanente healthcare system data.[55] The VE of mRNA-1273 against hospitalization was 72.4% for 3-doses and 88.5% for 4-doses. Studies in the US and UK also showed significant VE (60–70%) against BA.4/5-related hospitalization within 3–5 months after the last vaccination (third or fourth dose of the mRNA vaccine).[56-58] However, a study reported that significant VE could not be expected 6 months after the third dose or 3 months after the fourth dose of BNT162b2.[58] A study in South Africa conducted an elapsed time-stratified analysis for VE after the third dose of BNT162b2 against BA.4/5-related hospitalization, which showed a decrease in VE over time: 47.7% 3–4 months after the second dose, 26.3% 5–6 months after the second dose, 68.8% 1–2 months after the third dose, and 46.8% 3–4 months after the third dose.[59] The VE against omicron BA.4/5-related hospitalization declined rapidly after the first or second booster, suggesting a limited role of the original SARS-CoV-2-based vaccines.[55,58]

To maintain VE against the omicron subvariants, the two most widely used mRNA vaccines have been modified to include mRNA of the original SARS-CoV-2 and omicron subvariants (BA.1 or BA.4/5). These "bivalent" vaccines reportedly boost NAb titers, comparable to those induced by the original boosters, against the original SARS-CoV-2, while achieving superior titers against the omicron subvariants.[60,61] While the BA.1-modified bivalent vaccine induces NAb against BA.4/5, the increment is smaller (about 30%) than that against BA.1.[60-63] To maximize protection against the currently dominant variant, BA.4/5-modified bivalent vaccines have been developed. In a phase 2/3 study, including 511 participants (aged 19–89), Moderna's BA.4/5-modified bivalent vaccine (mRNA-1273.222) demonstrated superior NAb titers over mRNA-1273 with comparable safety profiles.[61] The geometric mean titer ratio was 5.11 (95% CI 4.10–6.36) for those with prior SARS-CoV-2 infection, and 6.29 (95% CI 5.27–7.51) for those without. An exploratory analysis (n=40) revealed a robust neutralizing activity against BQ.1.1, a subvariant that has been on the rise since this fall, despite an approximately five-fold drop in titers compared to against BA.4/5.[61] In contrast, a small-sized real-world study demonstrated no significant difference in NAb titers against BA.5 between BA.4/5-modified bivalent (n = 18) and original monovalent booster recipients (n = 15); a modest nonsignificant trend favoring the bivalent booster by a factor of 1.3 was seen.[64] The bivalent BA.4/5-modified VE might vary depending upon the recipient's past vaccination status and history of prior SARS-CoV-2 infection (elapsed time from past infection and variants). Actually, according to a recent report by US Centers for Disease Control and Prevention, the real-world VE of BA.4/5-modified bivalent vaccine against symptomatic SARS-CoV-2 infection was variable by age and the elapsed time since the last monovalent dose.[65] When administered at 2–3 months and ≥ 8 months after the last monovalent dose, the relative VE (compared to those who did not receive a bivalent booster) of a booster dose of BA.4/5-modified bivalent vaccine among ≥ 2 dose monovalent vaccine recipients was 30% and 56% for individuals aged 18–49 years, 31% and 48% for individuals aged 50–64 years, and 28% and 43% for individuals aged ≥ 65 years, respectively. Relative VE increased with time since the most recent monovalent vaccine dose. Compared to unvaccinated individuals, the absolute VE of a booster dose of BA.4/5-modified bivalent vaccine among persons who had received ≥ 2 monovalent doses was 43% (95% CI, 39–46%) for adults aged 18–49 years, 28% (95% CI, 22–33%) for adults aged 50–64 years, and 22% (95% CI, 15–29%) for the elderly aged ≥ 65 years, respectively.

ADVERSE EVENTS OF COVID-19 VACCINES IN KOREA

As COVID-19 vaccine rollout progressed across the country, a wide range of AEs were reported.[66-69] Aside from solicited AEs, the vast majority of them, especially serious AEs, were unlikely to be caused by vaccines. Investigations on AEs so far are reassuring, without significantly abnormal signals. Even so, the AEs provoked public backlash and became a major reason behind vaccine hesitancy.

According to the latest KDCA biweekly report, 3.72 cases of AEs were reported for every 1,000 vaccine doses, 3.6% of which were serious AEs.[11] People who received Ad26.COV2.S (5.88 per 1,000 doses) reported AEs the most often, followed by ChAdOx1 nCoV-19 (5.42 per 1,000 doses), mRNA-1273 (4.49 per 1,000 doses), BNT162b2 (3.03 per 1,000 doses), and NVX-CoV2373 (1.39 per 1,000 doses). Vaccine recipients in their 30s reported more cases of AEs (4.93 per 1,000 doses), and those over 80 had reported the least number of cases (1.98 per 1,000 doses). Women (4.71 per 1,000 doses) reported more AEs than did men (2.70 per 1,000 doses). Furthermore, the number of AE reports decreased with repeated vaccinations (first dose, 5.37 per 1,000 doses; second dose, 4.11 per 1,000 doses; third dose, 1.68 per 1,000 doses; fourth dose, 0.66 per 1,000 doses). The 3 most common AEs were headaches, myalgia, and dizziness, similar to clinical trial results.[13,14,70] During the first 8 months of national immunization, only 2 out of 835 deaths that occurred after vaccination had a causal relationship with vaccination.[71] The incidence of anaphylaxis was 5.8 per million doses, which is similar to the US and European Union statistics.[72]

Several hospitals analyzed vaccine AEs reported by their employees, who were largely young females.[73-77] All studies found that AEs were more commonly reported by females than males and by younger individuals than older individuals. Among 4,699 vaccinated HCWs in the studies which included AE severity data, only one person experienced serious AE.[75,77]

Children and adolescents reported fewer AEs than adults (5–11-year-olds, 0.79 per 1,000 doses; 12–18-year-olds, 3.20 per 1,000 doses).[11] KDCA reviewed AEs in adolescents aged 12–17 reported through February 2022.[78] Out of 12,216 AEs, there were 85 suspected cases of anaphylaxis, 74 suspected cases of myocarditis/pericarditis, 2 cases of suspected multisystem inflammatory syndrome, and 2 deaths. The KDCA concluded that the deaths were unrelated to vaccination. Similar to data in adults, the most commonly reported AEs were injection site pain, headaches, fatigue, and myalgia, consistent with the results from a clinical trial and a US surveillance study.[79,80]

However, the AE patterns of adolescents differed from those of the adults. Lee et al.[81] analyzed data from the Korean vaccine AE reporting system to compare the risk and types of AEs in adolescents (aged 12–15) with those in adults. Compared to adults, adolescents had a higher incidence of encephalitis/myelitis, convulsions, GBS, myocarditis/pericarditis, lymphadenopathy, lymphopenia, and multisystem inflammatory syndrome. Among these, the relative risk was highest for multisystem inflammatory syndrome (244.3, 95% CI, 31.27–1,908.38).

Neuroinflammatory diseases, such as GBS, have long been associated with vaccination, despite no clear evidence of a causal relationship outside of influenza vaccines.[82,83] The KDCA reviewed 101 alleged GBS cases reported up to August 19, 2022, and concluded that 22 of them were likely GBS, though there was insufficient evidence that vaccines were

responsible. Two out of 22 cases occurred after Ad26.COV2.S vaccination, and the rest occurred after receiving ChAdOx1 nCoV-19.

Some serious AEs deserve closer scrutiny for each vaccine product. Drawing particular attention were VITT and myocarditis/pericarditis after receiving adenoviral vector vaccines and mRNA vaccines, respectively. As of August 19, 2022, 4 out of 213 suspected VITT cases were causally related to vaccination, which translates to 9.74 cases per million doses of the adenoviral vector vaccine.[11] This number is lower than in the UK (15.8 per million doses) and Canadian (23 per million doses) statistics.[84,85] All 4 cases occurred after receiving ChAdOx1 nCoV-19: 3 after the first dose and 1 after the second dose. As of September 22, 2022, 749 cases (7.08 per million doses) of myocarditis/pericarditis have been identified after receiving an mRNA vaccine.[11] For comparison, the incidence was 4.6 per million doses in the US, 10–18 per million doses in the UK, and 11–17 per million doses in Canada.[84-86] To a lesser extent, these conditions also occurred in those who received adenoviral vector vaccines (28 cases; 1.28 per million doses) or recombinant nanoparticle vaccines (3 cases; 3.96 per million doses).[11] In these cases, the diagnosis of myocarditis/pericarditis was verified by KDCA but were not necessarily proven to be caused by vaccination.

As described so far, COVID-19 vaccines are safe and effective in both children and adults, justifying mass vaccination during the pandemic. Nevertheless, the National Vaccine Injury Compensation Program was launched to guarantee vaccine safety and to support people who experience rare AEs. HCWs or patients can report AEs online or via text messages and file a petition at the community health center. This is subsequently reviewed by the KDCA, Vaccine Injury Compensation Committee (composed of 15 members, including medical and legal experts), or local government within 12 weeks.[87,88] On July 19, 2022, a department dedicated to vaccine injury compensation was established.[89] Additionally, the maximum subsidy for COVID-19 vaccination-related AEs was raised from 30 million Korean Won (KRW) to KRW 50 million (approximately USD 37,800, as of November 15, 2022); for mortality, it was raised from KRW 50 million to KRW 100 million.[89] Also, patients with AEs without a clear causal relationship to vaccination (i.e. temporal association with vaccination, but insufficient causality data) can be compensated up to KRW 30 million since May 17, 2022.[87] As of August, 2022, 20,801 patients (15.9 per 100,000 vaccinations) have been compensated under the program.[88]

MASS VACCINATION AND THE MITIGATION OF PANDEMIC WAVES

The mass vaccination timeline through October 2, 2022, including cumulative vaccination rate, vaccine eligibility, case incidence, and excess mortality, is presented in **Fig. 2**. Shortly following the emergency approval of ChAdOx1 nCoV-19, the national immunization program began on February 26, 2021. Patients and HCWs in long-term care facilities and HCWs who directly provided care for COVID-19 patients were prioritized for vaccination.[90] Due to supply shortages, the ChAdOx1 nCoV-19 vaccine was administered at longer intervals (3 months) than tested in clinical trials to vaccinate a maximal number of people at least once. On April 8, 2021, ChAdOx1 nCoV-19 vaccinations were paused due to concerns over VITT. ChAdOx1 nCoV-19 vaccinations then resumed a few days later for individuals over 30 years old, due to concerns of a higher risk for VITT in younger people.[91,92] The age limit was revised to 50 years-old or above in July 2021.
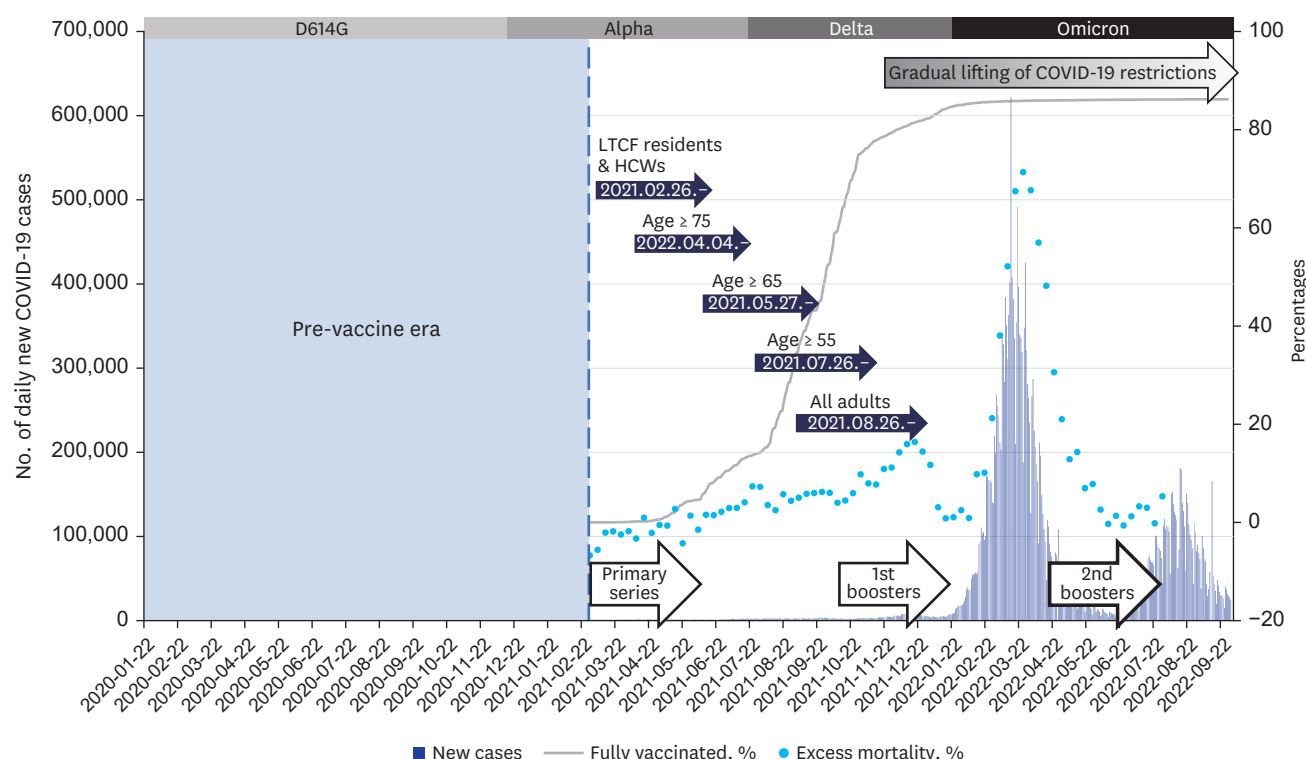
Fig. 2. Timeline of mass vaccination against COVID-19 in Korea. The blue vertical bars represent the number of daily new COVID-19 cases, the light blue dots represent weekly excess mortality (%), the grey curve represents the cumulative percentage of fully vaccinated individuals (i.e., completed primary series vaccination), and the dark blue arrows represent when each group became eligible for COVID-19 vaccines.
COVID-19 = coronavirus disease 2019, LTCF = long-term care facilities, HCWs = healthcare workers.

During the summer pandemic wave of 2021, led by the delta variant, the number of unvaccinated middle-aged patients overtook older patients in the COVID-19 wards and critical care units. Many of them had comorbidities such as obesity and diabetes.[93] Several months later, as the percentage of older patients rose again due to waning vaccine-induce immunity, KDCA distributed "booster shots," a third vaccine dose, to those who completed the primary series at least 4 months ago. After the intensive delivery of booster shots in December 2021, the number of cases and deaths declined again in January 2022.

Despite these efforts, the number of cases drastically rose since February 2022 as the notoriously immune-evading omicron variant became predominant.[94] In mid-April 2022, South Korea became the country with the second highest cumulative number of confirmed cases per capita among the G20 nations.[95] While case-fatality rates remained lower than in the previous pandemic waves, suppressed by vaccine-induced immunity, excess mortality rates were much higher, likely due to the sheer volume of COVID-19 cases overwhelming healthcare systems.[96]

It became obvious that vaccine-induced protection against symptomatic infection wanes within months. Since April 2022, people over 60, who accounted for the majority of severe infections and deaths, are encouraged to receive a booster.[38] As of September 29, 2022, 43.7% of people over 60 have received a fourth shot.[97] In late August 2022, the KDCA recommended the bivalent boosters, prioritizing high-risk individuals for the coming fall and winter.[98]

THE WAY FORWARD

Although the worst phase of the pandemic seems to be behind us, much work remains to be done. First, the need for additional vaccinations should be clarified. The target population and time interval between doses should also be addressed. Through repeated vaccination and past natural infections, long-lasting memory B cells and T cells may have already been induced in most people. When exposed to SARS-CoV-2, memory B cells can react immediately to produce NAbs against the virus. Moreover, through germinal center reaction, memory B cells and long-lived plasma cells further mature to generate NAbs with high affinity and diversity. These antibodies could better cross-neutralize variant viruses.[99] Additionally, T-cell immunity is more cross-reactive and longer sustained than humoral immunity, providing protection against severe SARS-CoV-2 infection for over a year.[100] Thus, it is unclear whether annual revaccination is necessary for the general population. Nonetheless, given that humoral immunity declines faster in older adults and chronically ill patients, repeated booster administration would be reasonable for populations at higher risk of morbidity and mortality.[101] Most probably, 1 or 2 boosters would be needed annually, depending on the accompanying medical conditions of the individual.

Second, the approval process for new COVID-19 vaccines, which are developed by replacing viral antigens of an approved vaccine platform should be simplified. The US Food and Drug Administration's emergency-use approval of BA.4/5-modified bivalent vaccine was based on preclinical data in the absence of clinical trials. This was possible due to the experience when developing beta-variant-modified and BA.1-modified bivalent vaccines; there was a high correlation between the clinical trial results and preclinical research with similar safety profiles. Such a review/approval system is based on preclinical data, including toxicity and immunogenicity, and has been applied to influenza vaccines for years.

Third, it is uncertain whether we need multivalent vaccines that contain several different SARS-CoV-2 variant antigens, as in the case of the influenza vaccine. It is difficult to predict because the COVID-19 pandemic is ongoing; however, unlike influenza, in which four types of viruses (A/H1N1, A/H3N3, B/Yamagata, and B/Victoria) are concurrently prevalent in each season, several SARS-CoV-2 variants might circulate at different times, which diminishes the usefulness of the multivalent vaccine. Nevertheless, given the frequent appearance of new SARS-CoV-2 variants, a multivalent vaccine could still be beneficial at increasing cross-reactive immunity. The usefulness of the multivalent vaccine will be further revealed through the upcoming adoption and subsequent evaluation of bivalent vaccines, as well as the monitoring of variant emergence frequencies in the course of transitioning to endemicity.

Fourth, effective communication is crucial to a pandemic response.[102] Even the best, groundbreaking research is useless if communicated poorly or left unapplied to the real world. Although anti-vaccine sentiment and vaccine hesitancy have always been present, they have risen to prominence in this once-in-a-century global disaster. Serious but rare AEs provoked fear, and breakthrough infections undermined public trust in vaccines, even while such infections were accounted for and the benefits of vaccination still far outweighed the risks.[103] Of particular concern are patients with comorbidities who are reluctant to get vaccinated against COVID-19, despite the recommendations of health authorities worldwide.[104] Additionally, while vaccines are the key component of a successful pandemic response, they alone can fail without non-pharmaceutical interventions like appropriate masking and social distancing. Reflecting on the surge of the omicron variant in early 2022 and the

subsequent rise in excess mortality to levels higher than the pre-vaccine era, the government had seemingly failed to deliver this message. On the other hand, authorities should also use caution when implementing coercive measures such as the Vaccine Pass. Communicating accessibly and reliably with the public, decoupling vaccines from politics, and delegating decisions to health experts will together help us respond to this and the next pandemics.

Finally, in preparation for the next pandemic, it is essential to make strategic and sufficient investments in vaccine research and development. In the absence of domestic vaccine development in the first half of 2021, South Korea had experienced delayed COVID-19 vaccine delivery, which could have led to preventable morbidity, mortality, economic loss, and a delayed return to normalcy. Up until August 2022, 10 vaccine candidates developed by 7 domestic companies have been approved to undergo clinical trial.[105] These include 3 mRNA vaccines, 1 DNA vaccine, 2 viral vector vaccines, and 4 recombinant vaccines. Only one recombinant nanoparticle vaccine out of the 10 candidates was approved in mid-2022, far behind the global competition. The rapid development of COVID-19 vaccines in the US and UK was facilitated by access to multiple vaccine platform technologies, experienced vaccine developers, and regulatory agencies that oversaw non-clinical to phase 1 clinical trials of numerous vaccines against various infectious diseases. However, South Korea's potential is now being recognized internationally. SK bioscience and Samsung Biologics are producing NVX-CoV2373 and mRNA-1273, respectively, as contract manufacturing organizations.[106,107] In February, 2022, the WHO designated South Korea as a new global biomanufacturing training hub to provide technical and hands-on experience to professionals from low- and middle-income countries.[108] A research ecosystem that connects clinical needs-based vaccine development to nonclinical and clinical trials should be established for continued progress.[109] This should occur alongside the promotion of ample investment in research and development. These lessons must be heeded, lest the same mistakes be repeated when the next pandemic strikes.

CONCLUSION

The COVID-19 pandemic has tested the healthcare system and the pandemic preparedness of South Korea. When the next pandemic arrives, we should be better at doing risk communications, vaccine development and distribution, while maintaining high adherence to vigilant surveillance, social distancing, and vaccination.

REFERENCES

1. Kim JY, Choe PG, Oh Y, Oh KJ, Kim J, Park SJ, et al. The first case of 2019 novel coronavirus pneumonia imported into Korea from Wuhan, China: implication for infection prevention and control measures. *J Korean Med Sci* 2020;35(5):e61.
   PUBMED | CROSSREF
2. WHO. Coronavirus disease (COVID-19) pandemic. https://www.who.int/europe/emergencies/situations/covid-19. Updated September 29, 2022. Accessed September 29, 2022.
3. Cumulative confirmed COVID-19 deaths. https://ourworldindata.org/coronavirus#explore-the-global-situation. Updated September 28, 2022. Accessed September 29, 2022.
4. COVID-19 National Emergency Response Center, Epidemiology and Case Management Team, Korea Centers for Disease Control and Prevention. Coronavirus disease-19: the first 7,755 cases in the Republic of Korea. *Osong Public Health Res Perspect* 2020;11(2):85-90.
   PUBMED | CROSSREF

5. Kang SJ, Jung SI. Age-related morbidity and mortality among patients with COVID-19. *Infect Chemother* 2020;52(2):154-64.
   PUBMED | **CROSSREF**

6. Kim M, Yoo JR, Heo ST, Lee HR, Oh H. Clinical characteristics and risk factors for severe disease of coronavirus disease 2019 in a low case fatality rate region in Korea. *Infect Chemother* 2021;53(4):718-29.
   PUBMED | **CROSSREF**

7. Agca M, Tuncay E, Yıldırım E, Yıldız R, Sevim T, Ernam D, et al. Is obesity a potential risk factor for poor prognosis of COVID-19? *Infect Chemother* 2021;53(2):319-31.
   PUBMED | **CROSSREF**

8. Hoang T, Tran Thi Anh T. Comparison of comorbidities in relation to critical conditions among coronavirus disease 2019 patients: a network meta-analysis. *Infect Chemother* 2021;53(1):13-28.
   PUBMED | **CROSSREF**

9. Kim Y, Kim SW, Chang HH, Kwon KT, Bae S, Hwang S. Significance and associated factors of long-term sequelae in patients after acute COVID-19 infection in Korea. *Infect Chemother* 2021;53(3):463-76.
   PUBMED | **CROSSREF**

10. Kim Y, Kim SE, Kim T, Yun KW, Lee SH, Lee E, et al. Preliminary guidelines for the clinical evaluation and management of long COVID. *Infect Chemother* 2022;54(3):566-97.
    PUBMED | **CROSSREF**

11. KDCA. COVID-19 vaccination safety report. https://ncv.kdca.go.kr/board.es?mid=a11707010000&bid=0032#. Updated September 25, 2022. Accessed September 29, 2022.

12. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. *Nat Rev Drug Discov* 2018;17(4):261-79.
    PUBMED | **CROSSREF**

13. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;383(27):2603-15.
    PUBMED | **CROSSREF**

14. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;384(5):403-16.
    PUBMED | **CROSSREF**

15. Rosa SS, Prazeres DM, Azevedo AM, Marques MP. mRNA vaccines manufacturing: challenges and bottlenecks. *Vaccine* 2021;39(16):2190-200.
    PUBMED | **CROSSREF**

16. Pillay J, Gaudet L, Wingert A, Bialy L, Mackie AS, Paterson DI, et al. Incidence, risk factors, natural history, and hypothesised mechanisms of myocarditis and pericarditis following covid-19 vaccination: living evidence syntheses and review. *BMJ* 2022;378:e069445.
    PUBMED | **CROSSREF**

17. Heymans S, Cooper LT. Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms. *Nat Rev Cardiol* 2022;19(2):75-7.
    PUBMED | **CROSSREF**

18. CDC. Update on myocarditis following mRNA COVID-19 vaccination. https://www.fda.gov/media/159007/download. Updated June 7, 2022. Accessed September 15, 2022.

19. EMA. New vaccine for prevention of Ebola virus disease recommended for approval in the European Union. https://www.ema.europa.eu/en/documents/press-release/new-vaccine-prevention-ebola-virus-disease-recommended-approval-european-union_en.pdf. Updated May 29, 2020. Accessed September 15, 2022.

20. WHO. Ebola virus disease - Democratic Republic of Congo External Situation Report 98. https://apps.who.int/iris/bitstream/handle/10665/332654/SITREP_EVD_DRC_20200623-eng.pdf. Updated June 23, 2020. Accessed September 15, 2022.

21. Yang TC, Millar JB, Grinshtein N, Bassett J, Finn J, Bramson JL. T-cell immunity generated by recombinant adenovirus vaccines. *Expert Rev Vaccines* 2007;6(3):347-56.
    PUBMED | **CROSSREF**

22. Fausther-Bovendo H, Kobinger GP. Pre-existing immunity against Ad vectors: humoral, cellular, and innate response, what's important? *Hum Vaccin Immunother* 2014;10(10):2875-84.
    PUBMED | **CROSSREF**

23. Liu X, Shaw RH, Stuart AS, Greenland M, Aley PK, Andrews NJ, et al. Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial. *Lancet* 2021;398(10303):856-69.
    PUBMED | **CROSSREF**

24. Vivaldi G, Jolliffe DA, Holt H, Tydeman F, Talaei M, Davies GA, et al. Risk factors for SARS-CoV-2 infection after primary vaccination with ChAdOx1 nCoV-19 or BNT162b2 and after booster vaccination with BNT162b2 or mRNA-1273: a population-based cohort study (COVIDENCE UK). *Lancet Reg Health Eur* 2022;22:100501.
PUBMED | **CROSSREF**

25. Menni C, May A, Polidori L, Louca P, Wolf J, Capdevila J, et al. COVID-19 vaccine waning and effectiveness and side-effects of boosters: a prospective community study from the ZOE COVID Study. *Lancet Infect Dis* 2022;22(7):1002-10.
PUBMED | **CROSSREF**

26. Pavord S, Scully M, Hunt BJ, Lester W, Bagot C, Craven B, et al. Clinical features of vaccine-induced immune thrombocytopenia and thrombosis. *N Engl J Med* 2021;385(18):1680-9.
PUBMED | **CROSSREF**

27. Acosta-Coley I, Cervantes-Ceballos L, Tejeda-Benítez L, Sierra-Márquez L, Cabarcas-Montalvo M, García-Espiñeira M, et al. Vaccines platforms and COVID-19: what you need to know. *Trop Dis Travel Med Vaccines* 2022;8(1):20.
PUBMED | **CROSSREF**

28. Dunkle LM, Kotloff KL, Gay CL, Áñez G, Adelglass JM, Barrat Hernández AQ, et al. Efficacy and safety of NVX-CoV2373 in adults in the United States and Mexico. *N Engl J Med* 2022;386(6):531-43.
PUBMED | **CROSSREF**

29. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. *N Engl J Med* 2021;385(13):1172-83.
PUBMED | **CROSSREF**

30. Song J, Choi W, Kwon K, Jung D, Choi H, Cheong H. *Phase 3 Study of Safety and Immunogenicity of GBP510 Vaccine Adjuvanted With AS03 in Adults (Abstract Number: 828), International Congress on Infectious Diseases (ISID 2022).* Brookline, MA, USA: International Society for Infectious Diseases; 2022.

31. Lim S, Lee Y, Kim DW, Park WS, Yoon JH, Lee JY. Anti-SARS-CoV-2 neutralizing antibody responses after two doses of ChAdOx1 nCoV-19 vaccine (AZD1222) in healthcare workers. *Infect Chemother* 2022;54(1):140-52.
PUBMED | **CROSSREF**

32. Kang YM, Minn D, Lim J, Lee K-D, Jo DH, Choe K-W, et al. Comparison of antibody response elicited by ChAdOx1 and BNT162b2 COVID-19 vaccine. *J Korean Med Sci* 2021;36(46):e311.
PUBMED | **CROSSREF**

33. Lee HJ, Jung J, Lee JH, Lee DG, Kim YB, Oh EJ. Comparison of six serological immunoassays for the detection of SARS-CoV-2 neutralizing antibody levels in the vaccinated population. *Viruses* 2022;14(5):946.
PUBMED | **CROSSREF**

34. Hyun H, Choi MJ, Heo JY, Seo YB, Nham E, Yoon JG, et al. Immunogenicity and reactogenicity of Ad26.COV2.S in Korean adults: a prospective cohort study. *J Korean Med Sci* 2022;37(27):e210.
PUBMED | **CROSSREF**

35. Bae S, Ko JH, Choi JY, Park WJ, Lim SY, Ahn JY, et al. Heterologous ChAdOx1 and Bnt162b2 vaccination induces strong neutralizing antibody responses against SARS-CoV-2 including delta variant with tolerable reactogenicity. *Clin Microbiol Infect* 2022;28(10):1390.e1-7.
PUBMED | **CROSSREF**

36. Hillus D, Schwarz T, Tober-Lau P, Vanshylla K, Hastor H, Thibeault C, et al. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1 nCoV-19 and BNT162b2: a prospective cohort study. *Lancet Respir Med* 2021;9(11):1255-65.
PUBMED | **CROSSREF**

37. KDCA. Analysis of the preventive effect of the fourth coronavirus disease vaccine dose in immunocompromised individuals and residents of elderly care hospitals and facilities. https://kdca.go.kr/board/board.es?mid=a20602010000&bid=0034&list_no=720134&act=view. Updated July 14, 2022. Accessed September 17, 2022.

38. KDCA. A fourth COVID-19 vaccination in 60+. http://ncov.kdca.go.kr/tcmBoardView.do?brdId=3&brdGubun=31&dataGubun=&ncvContSeq=6567&contSeq=6567&board_id=312&gubun=BDJ. Updated April 13, 2022. Accessed October 1, 2022.

39. Kang CK, Shin HM, Choe PG, Park J, Hong J, Seo JS, et al. Broad humoral and cellular immunity elicited by one-dose mRNA vaccination 18 months after SARS-CoV-2 infection. *BMC Med* 2022;20(1):181.
PUBMED | **CROSSREF**

40. Choi MJ, Choi JY, Hyun H, Nham E, Seong H, Yoon JG, et al. Cross-neutralization of omicron subvariants after heterologous NVX-CoV2373 boosters: comparison between prior SARS-CoV-2-infected and infection-naive individuals. *J Infect*. Forthcoming 2022. https://doi.org/10.1016/j.jinf.2022.09.018.
PUBMED | **CROSSREF**

41. Noh JY, Cheong HJ, Kim WJ, Choi JY, Lee HW, Kim SS, et al. Robust neutralizing antibody responses after single-dose BNT162b2 vaccination at long intervals from prior SARS-CoV-2 infection and ceiling effect with repeated vaccination. *J Infect* 2022;85(5):573-607.
PUBMED | **CROSSREF**

42. Ebinger JE, Fert-Bober J, Printsev I, Wu M, Sun N, Prostko JC, et al. Antibody responses to the BNT162b2 mRNA vaccine in individuals previously infected with SARS-CoV-2. *Nat Med* 2021;27(6):981-4.
PUBMED | **CROSSREF**

43. Krammer F, Srivastava K, Alshammary H, Amoako AA, Awawda MH, Beach KF, et al. Antibody responses in seropositive persons after a single dose of SARS-CoV-2 mRNA vaccine. *N Engl J Med* 2021;384(14):1372-4.
PUBMED | **CROSSREF**

44. Yi S, Choe YJ, Lim DS, Lee HR, Kim J, Kim YY, et al. Impact of national Covid-19 vaccination campaign, South Korea. *Vaccine* 2022;40(26):3670-5.
PUBMED | **CROSSREF**

45. Kim C, Kang G, Kang SG, Lee H. COVID-19 outbreak response at a nursing hospital in South Korea in the post-vaccination era, including an estimation of the effectiveness of the first shot of the Oxford-AstraZeneca COVID-19 vaccine (ChAdOx1-S). *Osong Public Health Res Perspect* 2022;13(2):114-22.
PUBMED | **CROSSREF**

46. KDCA. A Korea COVID-19 vaccine effectiveness (K-COVE) study published on clinical infectious diseases. https://www.korea.kr/news/pressReleaseView.do?newsId=156504574. Updated 2022. Accessed September 17, 2022.

47. KDCA. COV-EPI evaluation study in LTCF. https://kdca.go.kr/board/board.es?mid=a20602010000&bid=0034&list_no=719529&act=view. Updated May 12, 2022. Accessed September 17, 2022.

48. Thompson MG, Natarajan K, Irving SA, Rowley EA, Griggs EP, Gaglani M, et al. Effectiveness of a third dose of mRNA vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance - VISION network, 10 States, August 2021–January 2022. *MMWR Morb Mortal Wkly Rep* 2022;71(4):139-45.
PUBMED | **CROSSREF**

49. Zhu Y, Liu S, Zhang D. Effectiveness of COVID-19 vaccine booster shot compared with non-booster: a meta-analysis. *Vaccines (Basel)* 2022;10(9):1396.
PUBMED | **CROSSREF**

50. Kim SR, Kang HJ, Jeong HR, Jang SY, Lee JE, Kim DE, et al. Relative effectiveness of COVID-19 vaccination in healthcare workers: 3-dose versus 2-dose vaccination. *J Korean Med Sci* 2022;37(35):e267.
PUBMED | **CROSSREF**

51. Grewal R, Kitchen SA, Nguyen L, Buchan SA, Wilson SE, Costa AP, et al. Effectiveness of a fourth dose of covid-19 mRNA vaccine against the omicron variant among long term care residents in Ontario, Canada: test negative design study. *BMJ* 2022;378:e071502.
PUBMED | **CROSSREF**

52. Nordström P, Ballin M, Nordström A. Effectiveness of a fourth dose of mRNA COVID-19 vaccine against all-cause mortality in long-term care facility residents and in the oldest old: a nationwide, retrospective cohort study in Sweden. *Lancet Reg Health Eur* 2022;21:100466.
PUBMED | **CROSSREF**

53. June Choe Y, Yi S, Hwang I, Kim J, Park YJ, Cho E, et al. Safety and effectiveness of BNT162b2 mRNA Covid-19 vaccine in adolescents. *Vaccine* 2022;40(5):691-4.
PUBMED | **CROSSREF**

54. Hachmann NP, Miller J, Collier AY, Ventura JD, Yu J, Rowe M, et al. Neutralization escape by SARS-CoV-2 omicron subvariants BA.2.12.1, BA.4, and BA.5. *N Engl J Med* 2022;387(1):86-8.
PUBMED | **CROSSREF**

55. Tseng HF, Ackerson BK, Bruxvoort KJ, Sy LS, Tubert JE, Lee GS, et al. Effectiveness of mRNA-1273 against infection and COVID-19 hospitalization with SARS-CoV-2 Omicron subvariants: BA.1, BA.2, BA.2.12.1, BA.4, and BA.5. *medRxiv*. October 1, 2022. https://doi.org/10.1101/2022.09.30.22280573.
CROSSREF

56. Møller Kirsebom FC, Andrews N, Stowe J, Groves N, Chand M, Ramsay M, et al. Effectiveness of the COVID-19 vaccines against hospitalisation with omicron sub-lineages BA.4 and BA.5 in England. *Lancet Reg Health Eur* 2022;23:100537.
PUBMED | **CROSSREF**

57. Surie D, Bonnell L, Adams K, Gaglani M, Ginde AA, Douin DJ, et al. Effectiveness of monovalent mRNA vaccines against COVID-19-associated hospitalization among immunocompetent adults during BA.1/BA.2 and BA.4/BA.5 predominant periods of SARS-CoV-2 omicron variant in the United States - IVY network, 18 States, December 26, 2021–August 31, 2022. *MMWR Morb Mortal Wkly Rep* 2022;71(42):1327-34.
PUBMED | **CROSSREF**

58. Tartof SY, Slezak JM, Puzniak L, Hong V, Frankland TB, Ackerson BK, et al. BNT162b2 vaccine effectiveness against SARS-CoV-2 omicron BA.4 and BA.5. *Lancet Infect Dis* 2022;22(12):1663-5.
PUBMED | **CROSSREF**

59. Collie S, Nayager J, Bamford L, Bekker LG, Zylstra M, Gray G. Effectiveness and durability of the BNT162b2 vaccine against omicron sublineages in South Africa. *N Engl J Med* 2022;387(14):1332-3.
PUBMED | **CROSSREF**

60. Pfizer-BioNTech. Pfizer and BioNTech announce omicron-adapted COVID-19 vaccine candidates demonstrate high immune response against omicron. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-omicron-adapted-covid-19. Updated June 25, 2022. Accessed November 16, 2022.

61. Moderna. Moderna's BA.4/BA.5 targeting bivalent booster, mRNA-1273.222, meets primary endpoint of superiority against omicron variants compared to booster dose of mRNA-1273 in phase 2/3 clinical trial. https://investors.modernatx.com/news/news-details/2022/Modernas-BA.4BA.5-Targeting-Bivalent-Booster-mRNA-1273.222-Meets-Primary-Endpoint-of-Superiority-Against-Omicron-Variants-Compared-to-Booster-Dose-of-mRNA-1273-in-Phase-23-Clinical-Trial/default.aspx#. Updated November 14, 2022. Accessed November 16, 2022.

62. Pfizer-BioNTech. Pfizer/BioNTech COVID-19 omicron-modified bivalent vaccine. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-09-01/07-covid-swanson-508.pdf. Updated September 1, 2022. Accessed November 16, 2022.

63. Scheaffer SM, Lee D, Whitener B, Ying B, Wu K, Jani H, et al. Bivalent SARS-CoV-2 mRNA vaccines increase breadth of neutralization and protect against the BA.5 Omicron variant in mice. *Nat Med*. Forthcoming 2022. DOI: 10.1056/NEJMc2210093.
PUBMED | **CROSSREF**

64. Collier AY, Miller J, Hachmann NP, McMahan K, Liu J, Bondzie EA, et al. Immunogenicity of the BA.5 bivalent mRNA vaccine boosters. *bioRxiv*. October 25, 2022. https://doi.org/10.1101/2022.10.24.513619.
CROSSREF

65. Link-Gelles R, Ciesla AA, Fleming-Dutra KE, Smith ZR, Britton A, Wigegand RE, et al. Effectiveness of bivalent mRNA vaccines in preventing symptomatic SARS-CoV-2 infection — increasing community access to testing program, United States, September–November 2022. https://www.cdc.gov/mmwr/volumes/71/wr/mm7148e1.htm. Updated 2022. Accessed November 23, 2022.

66. Hyun H, Song JY, Seong H, Yoon JG, Noh JY, Cheong HJ, et al. Polyarthralgia and myalgia syndrome after ChAdOx1 nCOV-19 vaccination. *J Korean Med Sci* 2021;36(34):e245.
PUBMED | **CROSSREF**

67. Lee JH, Oh SM, Lee E, Bang JH, Park SW. Treatment for immune thrombocytopenia in coronavirus disease 2019 (COVID-19) infection after COVID-19 vaccination: a case report. *Infect Chemother* 2022;54(3):559-62.
PUBMED | **CROSSREF**

68. Park JW, Yu SN, Chang SH, Ahn YH, Jeon MH. Multisystem inflammatory syndrome in an adult after COVID-19 vaccination: a case report and literature review. *J Korean Med Sci* 2021;36(45):e312.
PUBMED | **CROSSREF**

69. Kang HS, Kim JE, Yoo JR, Oh H, Kim M, Kim YR, et al. Aseptic meningitis following second dose of an mRNA coronavirus disease 2019 vaccine in a healthy male: case report and literature review. *Infect Chemother* 2022;54(1):189-94.
PUBMED | **CROSSREF**

70. Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. *N Engl J Med* 2021;384(23):2187-201.
PUBMED | **CROSSREF**

71. Hwang I, Park K, Kim TE, Kwon Y, Lee YK. COVID-19 vaccine safety monitoring in Republic of Korea from February 26, 2021 to October 31, 2021. *Osong Public Health Res Perspect* 2021;12(6):396-402.
PUBMED | **CROSSREF**

72. Maltezou HC, Anastassopoulou C, Hatziantoniou S, Poland GA, Tsakris A. Anaphylaxis rates associated with COVID-19 vaccines are comparable to those of other vaccines. *Vaccine* 2022;40(2):183-6.
PUBMED | **CROSSREF**

73. Song JE, Oh GB, Park HK, Lee SS, Kwak YG. Survey of adverse events after the first dose of the ChAdOx1 nCoV-19 vaccine: a single-center experience in Korea. *Infect Chemother* 2021;53(3):557-61.
PUBMED | **CROSSREF**

74. Jeon M, Kim J, Oh CE, Lee JY. Adverse events following immunization associated with coronavirus disease 2019 vaccination reported in the mobile vaccine adverse events reporting system. *J Korean Med Sci* 2021;36(17):e114.
PUBMED | **CROSSREF**

75. Bae S, Lee YW, Lim SY, Lee JH, Lim JS, Lee S, et al. Adverse reactions following the first dose of ChAdOx1 nCoV-19 vaccine and BNT162b2 vaccine for healthcare workers in South Korea. *J Korean Med Sci* 2021;36(17):e115.
PUBMED | **CROSSREF**

76. Kim SH, Wi YM, Yun SY, Ryu JS, Shin JM, Lee EH, et al. Adverse events in healthcare workers after the first dose of ChAdOx1 nCoV-19 or BNT162b2 mRNA COVID-19 vaccination: a single center experience. *J Korean Med Sci* 2021;36(14):e107.
PUBMED | **CROSSREF**

77. Lee YW, Lim SY, Lee JH, Lim JS, Kim M, Kwon S, et al. Adverse reactions of the second dose of the BNT162b2 mRNA COVID-19 vaccine in healthcare workers in Korea. *J Korean Med Sci* 2021;36(21):e153.
PUBMED | **CROSSREF**

78. Kim S, Hwang I, Ko M, Kwon Y, Lee YK. Safety monitoring of COVID-19 vaccination among adolescents aged 12 to 17 years old in the Republic of Korea. *Osong Public Health Res Perspect* 2022;13(3):230-7.
PUBMED | **CROSSREF**

79. Frenck RW Jr, Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, et al. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. *N Engl J Med* 2021;385(3):239-50.
PUBMED | **CROSSREF**

80. Hause AM, Gee J, Baggs J, Abara WE, Marquez P, Thompson D, et al. COVID-19 vaccine safety in adolescents aged 12–17 years - United States, December 14, 2020–July 16, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70(31):1053-8.
PUBMED | **CROSSREF**

81. Lee CW, Sa S, Hong M, Kim J, Shim SR, Han HW. Adverse events and safety profile of the COVID-19 vaccines in adolescents: safety monitoring for adverse events using real-world data. *Vaccines (Basel)* 2022;10(5):744.
PUBMED | **CROSSREF**

82. Principi N, Esposito S. Vaccine-preventable diseases, vaccines and Guillain-Barre' syndrome. *Vaccine* 2019;37(37):5544-50.
PUBMED | **CROSSREF**

83. Salmon DA, Proschan M, Forshee R, Gargiullo P, Bleser W, Burwen DR, et al. Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis. *Lancet* 2013;381(9876):1461-8.
PUBMED | **CROSSREF**

84. Coronavirus vaccine - summary of Yellow Card reporting. https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting. Updated September 1, 2022. Accessed September 25, 2022.

85. Reported side effects following COVID-19 vaccination in Canada. https://health-infobase.canada.ca/covid-19/vaccine-safety/. Updated September 2, 2022. Accessed September 25, 2022.

86. Oster ME, Shay DK, Su JR, Gee J, Creech CB, Broder KR, et al. Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021. *JAMA* 2022;327(4):331-40.
PUBMED | **CROSSREF**

87. KDCA. National Vaccine Injury Compensation Program. https://ncv.kdca.go.kr/menu.es?mid=a12602000000. Updated 2022. Accessed November 16, 2022.

88. Kim J, Yoo Y, Bang E, Kim S. A comparison of the implementation of national COVID-19 vaccine injury compensation system. *Public Health Wkly Rep* 2022;15(39):2653-65.
CROSSREF

89. KDCA. Strengthening goverment support for vaccine injury compensation. https://ncov.kdca.go.kr/tcmBoardView.do?brdId=3&brdGubun=31&dataGubun=&ncvContSeq=6763&contSeq=6763&board_id=312&gubun=BDJ. Updated July 19, 2022. Accessed November 16, 2022.

90. Noh EB, Nam HK, Lee H. Which group should be vaccinated first?: a systematic review. *Infect Chemother* 2021;53(2):261-70.
PUBMED | **CROSSREF**

91. Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med* 2021;384(22):2124-30.
PUBMED | **CROSSREF**

92. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med* 2021;384(22):2092-101.
PUBMED | **CROSSREF**

93. Shi HJ, Nham E, Kim B, Joo EJ, Cheong HS, Hong SH, et al. Clinical characteristics and risk factors for mortality in critical coronavirus disease 2019 patients 50 years of age or younger during the delta wave: comparison with patients > 50 years in Korea. *J Korean Med Sci* 2022;37(22):e175.
PUBMED | **CROSSREF**

94. Liu L, Iketani S, Guo Y, Chan JF, Wang M, Liu L, et al. Striking antibody evasion manifested by the omicron variant of SARS-CoV-2. *Nature* 2022;602(7898):676-81.
PUBMED | **CROSSREF**

95. Cumulative confirmed COVID-19 cases per million people. https://ourworldindata.org/coronavirus#explore-the-global-situation. Updated September 29, 2022. Accessed September 30, 2022.

96. Excess mortality: Deaths from all causes compared to average over previous years. https://ourworldindata.org/grapher/excess-mortality-p-scores-average-baseline?country=~KOR. Updated July 31, 2022. Accessed October 1, 2022.

97. KDCA. Current status of COVID-19 outbreak and vaccination in Korea. http://ncov.kdca.go.kr/tcmBoardView.do?brdId=3&brdGubun=31&dataGubun=&ncvContSeq=6897&contSeq=6897&board_id=312&gubun=BDJ. Updated September 29, 2022. Accessed September 30, 2022.

98. KDCA. Booster plans against COVID-19, Winter 2022–2023: press release. http://ncov.kdca.go.kr/tcmBoardView.do?brdId=3&brdGubun=31&dataGubun=&ncvContSeq=6850&contSeq=6850&board_id=312&gubun=BDJ. Updated September 21, 2022. Accessed September 30, 2022.

99. Laidlaw BJ, Ellebedy AH. The germinal centre B cell response to SARS-CoV-2. *Nat Rev Immunol* 2022;22(1):7-18.
PUBMED | **CROSSREF**

100. Moss P. The T cell immune response against SARS-CoV-2. *Nat Immunol* 2022;23(2):186-93.
PUBMED | **CROSSREF**

101. Hägg S, Religa D. COVID vaccination in older adults. *Nat Microbiol* 2022;7(8):1106-7.
PUBMED | **CROSSREF**

102. Duong MC, Nguyen HT, Duong BT. Who influences the public intention to get a COVID-19 vaccine and what are the public references and concerns? A population survey in Vietnam. *Infect Chemother* 2021;53(4):753-66.
PUBMED | **CROSSREF**

103. Lamptey E. Should breakthrough SARS-CoV-2 infection affect our confidence in the COVID-19 vaccines? *Infect Chemother* 2021;53(4):676-85.
PUBMED | **CROSSREF**

104. Choi WS, Cheong HJ. COVID-19 vaccination for people with comorbidities. *Infect Chemother* 2021;53(1):155-8.
PUBMED | **CROSSREF**

105. MFDS. Domestic COVID-19 vaccine candidates in clinical trials. https://www.mfds.go.kr/docviewer/skin/doc.html?fn=20220805094804221.png&rs=/docviewer/result/co19vaccine01/1/1/202211. Updated November 1, 2022. Accessed November 18, 2022.

106. Novavax and SK bioscience Expand Manufacturing Agreement. https://ir.novavax.com/2021-12-23-Novavax-and-SK-bioscience-Expand-Manufacturing-Agreement. Updated December 23, 2021. Accessed November 18, 2022.

107. Moderna and Samsung Biologics Announce Agreement for Fill-Finish Manufacturing of Moderna's COVID-19 Vaccine. https://samsungbiologics.com/kr/media/company-news-view?boardSeq=1207&schBoardCtgryCcd=1&schString=&schBoardYear=&boardDtm=1621699200000&page=2. Updated August 13, 2021. Accessed November 18, 2022.

108. IVI. IVI to operate training courses for WHO global biomanufacturing training hub in Republic of Korea. https://www.ivi.int/ivi-to-operate-training-courses-for-who-global-biomanufacturing-training-hub-in-republic-of-korea/. Updated March 29, 2022. Accessed November 18, 2022.

109. Peck KR. Collaborative response to COVID-19 pandemic, and development of treatment guidelines. *Infect Chemother* 2021;53(1):151-4.
PUBMED | **CROSSREF**

110. Ministry of Food and Drug Safety. COVID-19 vaccines. https://www.mfds.go.kr/docviewer/skin/doc.html?fn=20221101084746428.hwp&rs=/docviewer/result/co19vaccine01/5/1/202211. Updated November 1, 2022. Accessed November 14, 2022.

111. Falsey AR, Sobieszczyk ME, Hirsch I, Sproule S, Robb ML, Corey L, et al. Phase 3 safety and efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 vaccine. *N Engl J Med* 2021;385(25):2348-60.
PUBMED | **CROSSREF**