Review Article

SARS-CoV-2 Immunity: Review of Immune Response to Infection and Vaccination

Rahnuma Ahmad

Abstract

After the last flu pandemic in 1918, the world has not faced a similar pandemic until now. However, it has been possible to identify the causative agent as well as its structure and function. The SARS-CoV-2 virus attacks the respiratory system, and the viral components like the spike protein and nucleocapsid protein produce an immune response in the host for viral elimination. The antigen can be recognized by or is presented to T cells. This results in neutralizing antibody production, cytokine secretion, and cytolysis. Although most infected individuals only suffer mild or moderate disease, some develop cytokine storms due to excess formation of cytokines resulting in ARDS, multiorgan failure, and DIC. The virus has mechanisms in place that can aid its escape from the host's immune response. Vaccine development has been underway around the globe to produce effective vaccines to limit morbidity and mortality from infection. Vaccines like mRNA vaccines encode the spike protein of coronavirus, and research has shown that antibodies developing from the vaccine were less affected by mutation in the spike protein of the virus than that developed from infection. The mRNA vaccine has modified nucleotide that limits the excessive formation of Interferons. Although various hurdles to overcome to vaccinate the world population effectively, vaccination may be essential to control the pandemic and a return to normalcy. This review highlights the current knowledge on the structure of the virus and the immune response triggered by the virus in infected individuals. It also reviews the currently available vaccines with their formulation, mechanism of immune response elicited.

Keywords: Pandemic, SARS-CoV-2, infection, Immune response, T helper cells, Neutralizing antibodies, Vaccine

Introduction

Since the identification of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) in December 2019, over 4 million of the world's population have succumbed to death after being infected with the virus by July of 2021. There are seven coronaviruses known to cause infection in humans: the 4 seasonal Coronaviruses causing self-limiting upper respiratory tract infections and 3 Coronaviruses with high pathogenicity (SARS-CoV-1, MERS [Middle East respiratory syndrome], and SARS-CoV-2). These highly pathogenic Coronaviruses, SARS-CoV-1, MERS, and SARS-CoV-2, have emerged in 2003, 2012, and 2019 respectively. There is limited knowledge regarding the immunity to all Corona viruses. Individuals who suffer from seasonal Coronaviruses tend to develop immunity for about one year, while the quantity of antibodies acquired from infection with SARS-CoV-1 and MERS significantly decreases 2-3 years following the onset of symptom individuals susceptible to reinfection. The understanding of the immunity against SARS-CoV-2 has been developing through sero surveillance studies conducted during the pandemic and evaluating B- and T-cell responses to SARS-CoV-2 among convalescent subjects with varying degrees of severity of disease. The diminution of the pandemic of COVID-19 is dependent on the world population acquiring immunity through infection with or by receiving the vaccination.
vaccination against this virus. However, it has been observed that human beings are susceptible to repeated infection with ‘common cold’ coronaviruses. One of the reasons for such reinfection is that these coronaviruses tend to alter their structure to escape the immunity given by antibodies developed from previous infection. Similarly, SARS-CoV-2 has been evolving and generating new lineages with decreased neutralization by antibodies produced from prior infection and vaccination. Although the human immune system offers considerable protection against infection and severe forms of the disease caused by the new variants, viral evolution will eventually overcome this protection of immunity against reinfection.

Effective vaccines may be the answer to controlling the pandemic. Initiatives have therefore been underway for the rapid development of vaccines. The licensed vaccines at present for SARS-CoV-2 have been based on the SARS-CoV-1 and MERS experience. However, the developed vaccines for SARS-CoV-1 and MERS did not progress further than phase 1 of clinical trials. At present, there are more than 270 COVID-19 vaccine development in progress that includes more than 90 in clinical trial and include Nucleic acid vaccines (RNA and DNA), whole-cell inactivated virus, human and simian replication-deficient and replication-competent adenoviral-vectored vaccines and whole-cell inactivated vaccines CoronaVac (Sinovac Biotech), WIBP-CorV (Sinopharm). The vaccine candidates include Westpac Biopharma, OSE Therapeutics, Jiangsu Rec-Biotechnology/IQVIA, Sanofi/GSK, ReiThera/Leukocare, Scientific and Technological Research Council of Turkey, Moderna, Pfizer/BioNTech, AstraZeneca, Janssen Vaccines, Gamaleya Research Institute, Sinovac, Sinopharm, Anhui Zhifei Longcom Biopharmaceutical and Dynavax.

Some of the drawbacks of the approved vaccines include challenges of logistics, slow roll-out, cold chain, and ultracold chain needed for mRNA-based vaccines. This need for ultra-cold chain impedes rolling out these mRNA vaccines in middle and low-income countries. Also, the continuing viral evolution results in mutations that lower immunity induced through vaccination. As observed in other pathogens, escape mutant development may accelerate in the population due to vaccine-induced immune selection.

Methods

For this review, a literature search was performed using PubMed, Google search engine, Google scholar. Reference lists in the relevant articles were hand-searched to find more articles related to the topic. Keywords used to search related articles were ‘SARS-CoV-2’, ‘COVID-19’, ‘Pandemic’, ‘Immune Response,’ ‘Vaccination,’ ‘Vaccine.’

Structure of SARS-CoV-2 Virus

The Coronavirus has been named such because of the spikes that project from the virus’s envelope, which gives it a crown-like shape. The envelope has a lipid bilayer which is derived from the host’s cell membrane and also has 4 structural proteins that include spike (S), nucleoprotein (N), envelope (E), and membrane (M) (Figure 1). The virus recognizes the angiotensin-converting enzyme 2 to attach to cells, particularly the respiratory epithelial cells of the host.

Methods

For this review, a literature search was performed using PubMed, Google search engine, Google scholar. Reference lists in the relevant articles were hand-searched to find more articles related to the topic. Keywords used to search related articles were ‘SARS-CoV-2’, ‘COVID-19’, ‘Pandemic’, ‘Immune Response,’ ‘Vaccination,’ ‘Vaccine.’

Structure of SARS-CoV-2 Virus

The Coronavirus has been named such because of the spikes that project from the virus’s envelope, which gives it a crown-like shape. The envelope has a lipid bilayer which is derived from the host’s cell membrane and also has 4 structural proteins that include spike (S), nucleoprotein (N), envelope (E), and membrane (M) (Figure 1). The virus recognizes the angiotensin-converting enzyme 2 to attach to cells, particularly the respiratory epithelial cells of the host.

**Methods**

For this review, a literature search was performed using PubMed, Google search engine, Google scholar. Reference lists in the relevant articles were hand-searched to find more articles related to the topic. Keywords used to search related articles were ‘SARS-CoV-2’, ‘COVID-19’, ‘Pandemic’, ‘Immune Response,’ ‘Vaccination,’ ‘Vaccine.’

**Structure of SARS-CoV-2 Virus**

The Coronavirus has been named such because of the spikes that project from the virus’s envelope, which gives it a crown-like shape. The envelope has a lipid bilayer which is derived from the host’s cell membrane and also has 4 structural proteins that include spike (S), nucleoprotein (N), envelope (E), and membrane (M) (Figure 1). The virus recognizes the angiotensin-converting enzyme 2 to attach to cells, particularly the respiratory epithelial cells of the host.

**Methods**

For this review, a literature search was performed using PubMed, Google search engine, Google scholar. Reference lists in the relevant articles were hand-searched to find more articles related to the topic. Keywords used to search related articles were ‘SARS-CoV-2’, ‘COVID-19’, ‘Pandemic’, ‘Immune Response,’ ‘Vaccination,’ ‘Vaccine.’

**Structure of SARS-CoV-2 Virus**

The Coronavirus has been named such because of the spikes that project from the virus’s envelope, which gives it a crown-like shape. The envelope has a lipid bilayer which is derived from the host’s cell membrane and also has 4 structural proteins that include spike (S), nucleoprotein (N), envelope (E), and membrane (M) (Figure 1). The virus recognizes the angiotensin-converting enzyme 2 to attach to cells, particularly the respiratory epithelial cells of the host.

**Methods**

For this review, a literature search was performed using PubMed, Google search engine, Google scholar. Reference lists in the relevant articles were hand-searched to find more articles related to the topic. Keywords used to search related articles were ‘SARS-CoV-2’, ‘COVID-19’, ‘Pandemic’, ‘Immune Response,’ ‘Vaccination,’ ‘Vaccine.’

**Structure of SARS-CoV-2 Virus**

The Coronavirus has been named such because of the spikes that project from the virus’s envelope, which gives it a crown-like shape. The envelope has a lipid bilayer which is derived from the host’s cell membrane and also has 4 structural proteins that include spike (S), nucleoprotein (N), envelope (E), and membrane (M) (Figure 1). The virus recognizes the angiotensin-converting enzyme 2 to attach to cells, particularly the respiratory epithelial cells of the host.

**Methods**

For this review, a literature search was performed using PubMed, Google search engine, Google scholar. Reference lists in the relevant articles were hand-searched to find more articles related to the topic. Keywords used to search related articles were ‘SARS-CoV-2’, ‘COVID-19’, ‘Pandemic’, ‘Immune Response,’ ‘Vaccination,’ ‘Vaccine.’

**Structure of SARS-CoV-2 Virus**

The Coronavirus has been named such because of the spikes that project from the virus’s envelope, which gives it a crown-like shape. The envelope has a lipid bilayer which is derived from the host’s cell membrane and also has 4 structural proteins that include spike (S), nucleoprotein (N), envelope (E), and membrane (M) (Figure 1). The virus recognizes the angiotensin-converting enzyme 2 to attach to cells, particularly the respiratory epithelial cells of the host.
Immune response when infected with SARS-CoV-2

Both humoral and cellular immunity appears to be involved in the immune response to recover from SARS-CoV-2 infection (Figure 2)\(^{39,41}\). Antibodies having broad function have been detected at an early stage of infection in subjects hospitalized with COVID-19. These antibodies are aimed at the spike (S) protein of SARS-CoV-2 and have shown a correlation with the survival of the patients\(^{42}\). Most of the individuals develop S-protein-targeted neutralizing antibodies (Nabs) following infection. The extent of NAb response has been correlated with viral load and age as the response is higher in individuals with more severe disease and older adult subjects compared to younger adult subjects\(^{43-46}\). It has been observed, in studies carried out on the rhesus macaque model, that the Nabs show the strongest correlation with protection\(^{26,47}\). Thus vaccines produced for SARS-CoV-2 must be able to cause NAb response\(^{48}\). Non-Nabs can also perform a protective function, including antibody-dependent natural killer cell activation, antibody-dependent cellular cytotoxicity, and antibody-dependent phagocytosis\(^{26,42,49}\). On the other hand, antibodies that promote inflammation may be responsible for cytokine storms leading to severe forms of the disease\(^{50,51}\). Even though most individuals suffering from COVID-19 having mild and moderate disease recover within one week, some suffer severe pneumonia following cytokine storm in the second week. They develop Acute Respiratory Distress Syndrome, disseminated intravascular coagulation, and multiorgan failure within the 3rd week. The cytokine storm is caused by the activation of white blood cells in large quantities, including B cells, T cells, NK cells, macrophage, dendritic cells with the release of the high amount of inflammatory cytokines like IFN, IL 1β, IL 6, IL 12, IL17\(^{52-54}\).

Mucosal immunity is perhaps the critical factor in the prevention of infection with SARS-CoV-2. However, there is little available information regarding the response of mucosal antibody in COVID-19\(^{48}\). IgA specific to SARS-CoV-2 has been found in saliva and nasal washes of subjects in convalescence that may lower spread of infection from person to person by antibodies’ Fc dependent effector function and neutralization\(^{48}\). T lymphocytes take part in the host response to this infection by killing cells that are infected, giving support for B cell functioning and antibody response and lowering vaccine-induced enhanced disease risk\(^{56,57}\). A more vigorous clonal expansion of CD8+ T cells in blood and lungs has been noted in the milder form of the disease and recovery\(^{58,59}\). In recovered patients, virus-specific CD4+ and CD8+ T cells, including memory CD8+ T cells, have been found\(^{48,60}\). However, their significance in protecting against reinfection remains unresolved\(^{60-63}\). T helper 1 cells that produce interferon-\(\alpha\) are found in acute infection and a less severe form of the disease\(^{41,64}\). It has been observed that individuals

Figure 2: Immune response to SARS-CoV-2 infection
who have interferon-secreting T helper cells against nuclear proteins, membrane proteins, and S protein of SARS-CoV-2 are better protected from COVID-19 infection\textsuperscript{65}. The vaccines for COVID-19 intend to induce responses similar to T helper cell phenotype\textsuperscript{68}. The more efficient response of T follicular cells helps to increase the number of plasmablasts and increase antibody. Human and animal studies have noted that a strong cytotoxic CD8+ T cell and T helper cell 1 biased CD4+ effector response would provide protection against COVID-19 \textsuperscript{67}. SARS-CoV-2, similar to other respiratory RNA viruses, can adopt multiple mechanisms to evade the innate immune response\textsuperscript{67,68}. The various mechanisms include type I interferon response inhibition\textsuperscript{69-71} at different points, including impairment of viral RNA recognition\textsuperscript{72,73}, reduction of nuclear translocation of transcription factors of inflammation like IRF3, STAT1, and IRF7\textsuperscript{72,74} and STAT1 and STAT2 phosphorylation suppression\textsuperscript{75,76}. Even though several components of innate immunity are significant for protection against COVID-19, type I and type III interferons are centrally relevant\textsuperscript{77,78}.

**Vaccines Formulation and Mechanism of Immune Activation**

The vaccines that Moderna and Pfizer have developed apply mRNA technology and lipid nanoparticle system of delivery; AstraZeneca, Johnson, and Johnson, Sputnik V uses recombinant technology in which DNA is transferred into non-replicating adenovirus vector\textsuperscript{79,82}. Since the SARS-CoV-2 spike protein S is the primary target for the neutralizing antibodies formed from natural infection and the monoclonal antibodies, both the adenovirus and mRNA vaccines encode this spike protein. The efficacy of Moderna (mRNA-1273) and Pfizer/BioNTech mRNA vaccines for protection against COVID-19 have been noted to be 90-95%\textsuperscript{79,80}; the adenovirus vaccine and Sputnik V displayed an efficacy of about 70% and 91%, respectively\textsuperscript{81,82}. When measured in blood 2 to 4 weeks after inoculation, both types of vaccine were observed to produce significant titers of neutralizing antibody and virus-specific T cell response\textsuperscript{83,84}. A vaccine needs pathogen-specific immunogen and adjuvant for immune response, in which the adjuvant stimulates the innate immune system and gives secondary signal activation of T cells that is part of adaptive immune response\textsuperscript{85}. The mRNA present in mRNA vaccines acts as an immunogen (encode a viral protein) and adjuvant, as RNA has immune-stimulatory properties. Once the single-stranded and double-stranded RNA enters the cell, they are recognized by the cytosolic and endosomal innate sensors that form a crucial component of the innate immune response. TLR3 and TLR7 (endosomal Toll-like receptors) bind to single-stranded RNA and inflammasome components in cytosols like RIG-1, NOD2, MDA5, and PKR bind to both single-stranded and double-stranded RNA, leading to cellular activation and formation of inflammatory mediators and type I interferon\textsuperscript{86,87}. The vitro transcribed single-stranded mRNA of the current vaccines contain modified nucleotide, which decreases TLR and immune sensor binding and thus reduces the excessive formation of type I interferon and inhibiting cellular translation \textsuperscript{86}. The mRNA is delivered to lymphatics, and protein translation occurs in the lymphnodes\textsuperscript{85,87}. The lipid nanoparticles are engulfed by the dendritic cells in the lymph nodes and are eventually form antigen and present to the T cells for adaptive immune response activation\textsuperscript{88}. There is the secretion of different cytokines for T cell proliferation and chemokines for T cells recruitment\textsuperscript{89,90}.

The mRNA vaccines encode the SARS CoV-2 ectodomain with transmembrane anchor and stabilizing S-2P mutation. Therefore, it may elicit antibodies that may be more specific than acquired through natural infection due to spike variation or immune response divergence to the mRNA vaccine instead of infection\textsuperscript{91,92}. A study performed in the USA in 2021 shows the difference in the specificity of serum polyclonal antibodies acquired by infection compared to that acquired vaccination with mRNA-1273 observed antibodies elicited by the vaccine are less affected by single spike receptor-binding domain (RBD) mutation than antibodies elicited by infection. Vaccine elicited antibodies were also noted to bind more broadly across the receptor-binding domain, whereas infection-elicited receptor binding domain antibodies focused on an epitope that includes the E484 site. This makes neutralization by vaccine more resistant to RBD mutation. In vaccinated individuals, the antibody response is more homogeneous than convalescent individuals. In those vaccinated, a more uniform neutralizing titer, RBD binding titer, neutralization amount derived from RBD binding antibodies, and mutation on neutralization were observed compared to those convalescent\textsuperscript{93}. The mRNA-lipid nanoparticle vaccine produces a different antigen presentation kinetics than viral infection\textsuperscript{94,95}. Also, the distribution of antibody
isotopes elicited by mRNA vaccination is different, and fewer of these antibodies cross-react to common cold coronaviruses when compared to that developed through COVID-19 infection.

The Adenovirus vaccine, once injected, targets macrophages and Dendritic cells and enhances innate immune response by stimulation of pattern recognition receptors, mainly TLR9, which then causes Type 1 interferon secretion. The Dendritic cells and other cells that secrete Type 1 interferon sends inflammatory and antigenic signals to T cells in lymph nodes activating T cells specific to S protein and stimulates an adaptive immune response against SARS-CoV-2.

A community-based survey carried out in the United Kingdom between December 2020 and May 2021 to assess the effectiveness of COVID-19 vaccination (Pfizer-Biotech; BNT162b2 and Oxford-AstraZeneca; ChAdOx1) for the prevention of SARS-CoV-2 infections observed a reduction in the number of new SARS-CoV-2 infections and the maximum benefit was obtained after receiving 2 doses of vaccine and against high viral load and symptomatic infection.

Conclusion

It has been observed from early human trial results that both mRNA and Adenovirus vaccines cause the production of virus-specific neutralizing antibodies and IgG against S protein. Vaccination can limit SARS-CoV-2 spread and lead to a return to normalcy. However, the efficacy of vaccines is potentially limited by the appearance of S protein variants. Reservoirs of the disease within human beings and other animals may eradicate the SARS-CoV-2 virus challenge. Formulation of promising vaccines can fortify the immune system and perhaps lead to curtailing the virus and a path out of the world’s pandemic.

Recommendation

Formulation of new vaccines with variant S sequence and SARS-CoV-2 proteins can be produced. In order to overcome persistent virus strains, annual SARS-CoV-2 vaccination may be given. Mutant S protein-containing mRNAs can be synthesized and added to LNP carriers and administered in mRNA vaccines. Heterogeneity of immune response to vaccination may be observed when vaccinating mass populations on a global scale. Enhancement of T cell immunity may also be produced by developing and administering vaccines with self-replicating mRNA. Vaccines may therefore be optimized in accordance with the age and immune condition of the individuals.

Consent for Publication

The author reviewed and approved the final version and has agreed to be accountable for all aspects of the work, including issues related to accuracy or integrity.

Acknowledgment

The author expresses hey gratitude to Professor (Dr.) Mainul Haque, The Unit of Pharmacology, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), Kem Perdana Sungai Besi, 57000 Kuala Lumpur, Malaysia, for his kind advice and guidance in the course of writing this article. The author also expresses her gratitude to Faiza Binte Mozammel, Photographer and editor, student of the Department of BBA, Independent University Bangladesh, Bashundhara, Dhaka, Bangladesh, for her kind effort and time regarding image development and editing.

Author Contribution

The author has developed the concept, study design, execution, data acquisition, analysis, and interpretation. The author performed the drafting, revising, and critical review of the article and gave the final approval of the version to be published: has agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

Funding

This paper is not funded.

Disclosure

The author declares not having any financial involvement or affiliations with any organization, association, or entity directly or indirectly with the subject matter or materials presented in this article. This also includes honoraria, expert testimony, employment, ownership of stocks or options, patents or grants received or pending, or royalties.
References

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. Updated Jul 29, 2021. Available at https://covid19.who.int/ [Accessed Jul 29, 2021]

2. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. *Acta Biomed*. 2020; 91(1):157-60. doi: 10.23750/abm.v91n1.9397

3. Callaway E, Cyranoski D, Mallapaty S, Stoye E, Tollefson J. The coronavirus pandemic in five powerful charts. *Nature*. 2020;579(7800):482-83. doi: 10.1038/d41586-020-00758-2.

4. Poland GA, Ovsyannikova IG, Kennedy RB. SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates. *Lancet*. 2020;396(10262):1595-1606. doi: 10.1016/S0140-6736(20)32137-1

5. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronavirus - drug discovery and therapeutic options. *Nat Rev Drug Discov*. 2016;15(5):327-47. doi: 10.1038/nrd.2015.37

6. Wu LP, Wang NC, Chang YH, Tian XY, Na DY, Zhang LY, et al. Duration of antibody responses after severe acute respiratory syndrome. *Emerg Infect Dis*. 2007;13(10):1562-4. doi: 10.3201/eid1310.070576

7. Payne DC, Iblan I, Rha B, Alqasrawi S, Haddadin A, Al Nsour M, et al. Persistence of Antibodies against Middle East Respiratory Syndrome Coronavirus. *Emerg Infect Dis*. 2016;22(10):1824-6. doi: 10.3201/eid2210.160706

8. Edridge AWD, Kaczorowska J, Hoste ACR, Bakker M, Klein M, Loens K, et al. Seasonal coronavirus protective immunity is short-lasting. *Nat Med*. 2020;26(11):1691-93. doi: 10.1038/s41591-020-1083-1

9. Fergie J, Srivastava A. Immunity to SARS-CoV-2: Lessons Learned. *Front Immunol*. 2021;12:654165. doi: 10.3389/fimmu.2021.654165

10. Swelum AA, Shafi ME, Albaqami NM, El-Saadony MT, Elsify A, Abdo M, et al. COVID-19 in Human, Animal, and Environment: A Review. *Front Vet Sci*. 2020;7:578. doi: 10.3389/fvs.2020.00578

11. Eguia RT, Crawford KHD, Stevens-Ayers T, Kelnhofer-Millevolle L, Greninger AL, Englund JA, et al. Human coronavirus evolves antigenically to escape antibody immunity. *PLoS Pathog*. 2021;17(4):e1009453. doi: 10.1371/journal.ppat.1009453

12. Cele S, Gazy I, Jackson L, Hwa SH, Tegally H, Lustig G, et al. Escape of SARS-CoV-2 S01Y.V2 from neutralization by convalescent plasma. *Nature*. 2021;593(7857):142-46. doi: 10.1038/d41586-021-03471-w

13. Garcia-Beltran WF, Lam EC, St-Denis K, Nitido AD, Garcia ZH, Hauser BM, et al. Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. *Cell*. 2021;184(9):2372-83.e9. doi: 10.1016/j.cell.2021.03.013

14. Wang Z, Schmidt F, Weisblum Y, Muecksch F, Barnes CO, Finkin S, et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. *Nature*. 2021;592(7855):616-22. doi: 10.1038/s41586-021-03324-6

15. Chen RE, Zhang X, Case JB, Winkler ES, Liu Y, VanBlargan LA, et al. Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies. *Nat Med*. 2021;27(4):7:17-726. doi: 10.1038/s41591-021-01294-w

16. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Oosthuysen B, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. *Nat Med*. 2021;27(4):622-625. doi: 10.1038/s41591-021-01285-x

17. Novavax. Novavax COVID-19 Vaccine Demonstrates 90% Overall Efficacy and 100% Protection Against Moderate and Severe Disease in PREVENT-19 Phase 3 Trial. Updated Jun 14, 2021. Available at https://ir.novavax.com/2021-06-14-Novavax-COVID-19-Vaccine-Demonstrates-90-Overall-Efficacy-and-100-Protection-Against-Moderate-and-Severe-Disease-in-PREVENT-19-Phase-3-Trial [Accessed Jul 29, 2021]

18. Pfizer inc. Pfizer and BioNTech confirm high efficacy and no serious safety concerns through up to six months following the second dose in updated topline analysis of landmark COVID-19 vaccine study.2021.Updated Apr 1, 2021. Available at https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-confirm-high-efficacy-and-no-serious [Accessed Jul 29, 2021]

19. Greaney AJ, Loes AN, Gentles LE, Crawford KHD, Starr TN, Malone KD, et al. Antibodies elicited by mRNA-1273 vaccination bind more broadly to the receptor-binding domain than do those from SARS-CoV-2 infection. *Sci Transl Med*. 2021;13(600):eaai9915. doi: 10.1126/scitranslmed.aai9915

20. Diamond MS, Pierson TC. The Challenges of Vaccine Development against a New Virus during a Pandemic. *Cell Host Microbe*. 2020;27(5):699-703. doi: 10.1016/j.chom.2020.04.021

21. Thanh Le T, Andreadakis Z, Kumar A, Gómez Román R, Tollefson S, Saville M, et al.The COVID-19 vaccine development landscape. *Nat Rev Drug Discov*. 2020;19(5):305-306. doi: 10.1038/d41573-020-00073-5

22. World Health Organisation. COVID-19 vaccine tracker and landscape. Updated Jul 27, 2021. Available from URL https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines [Accessed Jul 29, 2021]

23. Amanat F, Krammer F. SARS-CoV-2 Vaccines: Status Report. *Immunity*. 2020;52(4):583-589. doi: 10.1016/j.immuni.2020.03.007

24. Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurman A, Lockhart S, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. *Nature*. 2020
25. Corbett KS, Edwards DK, Leist SR, Abiona OM, Boyoglu-Barnum S, Gillespie RA, et al. SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. Nature. 2020; 586(7830):579-83. doi: 10.1038/s41586-020-2639-4

26. Yu J, Tostanoski LH, Peter L, Mercado NB, McMahan K, Mahrokhian SH, et al. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. Science. 2020; 369(6505):806-11. doi: 10.1126/science.abc6284

27. Smith TRF, Patel A, Ramos S, Elwood D, Zhu X, Yan J, et al. Immunogenicity of a DNA vaccine candidate for COVID-19. Nat Commun. 2020; 11(1):2601. doi: 10.1038/s41467-020-16505-0

28. Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science. 2020; 369(6499):77-81. doi: 10.1126/science.abc1932.

29. Wang H, Zhang Y, Huang B, Deng W, Quan Y, Wang W, et al. Development of an Inactivated Vaccine Candidate, BBIBP-CoV, with Potent Protection against SARS-CoV-2. Cell. 2020; 182(3):713-721.e9. doi: 10.1016/j.cell.2020.06.008

30. Zhu FC, Li YH, Guan XH, Hou LH, Wang WJ, Li JX, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomized, first-in-human trial. Lancet. 2020; 395(10240):1845-1854. doi: 10.1016/S0140-6736(20)31208-3

31. van Doremalen N, Lambe T, Spencer A, Belij-Rammerstorfer S, Purushotham JN, Port JR, et al. ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques. Nature. 2020; 586(7830):579-582. doi: 10.1038/s41586-020-2608-y

32. Regulatory Focus. COVID-19 Vaccine Tracker. Updated Jul 23, 2021. Accessed Jul 27, 2021, Available at https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker [Accessed Jul 27, 2021]

33. UNICEF. COVID-19 vaccine deliveries: “The major challenge is the need for speed”. 2021. Accessed July 31, 2021. Available at https://www.unicef.org/supply/covid-19-vaccine-deliveries-major-challenge-need-speed [Accessed July 31, 2021]

34. Abdool Karim SS, de Oliveira T. New SARS-CoV-2 Variants - Clinical, Public Health, and Vaccine Implications. N Engl J Med. 2021;384(19):1866-68. doi: 10.1056/NEJMc2100362

35. Ganusov VV, Antia R. Imperfect vaccines and the evolution of pathogens causing acute infections in vertebrates. Evolution. 2006;60(5):957-69.

36. Weigand MR, Peng Y, Cassidy PK, Loparev VN, Johnson T, Jueng P, et al. Complete Genome Sequences of Bordetella pertussis Isolates with Novel Pertactin-Deficient Deletions. Genome Announc. 2017; 5(37):e00973-17. doi: 10.1128/genomeA.00973-17.

37. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020; 579(7798):270-273. doi: 10.1038/s41586-020-1217-7

38. Kim YI, Kim SG, Kim SM, Kim EH, Park SJ, Yu KM, et al. Infection and Rapid Transmission of SARS-CoV-2 in Ferrets. Cell Host Microbe. 2020;27(5):704-709.e2. doi: 10.1016/j.chom.2020.03.023

39. Gudbjartsson DF, Norddahl GL, Melsted P, Gunnarsdottir K, Holm H, Eythorsson E, et al. Humoral Immune Response to SARS-CoV-2 in Iceland. N Engl J Med. 2020; 383(18):1724-1734. doi: 10.1056/NEJMoa2026116

40. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med. 2020; 26(10):1636-1643. doi: 10.1038/s41591-020-1051-9

41. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020; 130(5):2620-29. doi: 10.1172/JCI137244.

42. Atyeo C, Fischinger S, Zohar T, Slein MD, Burke J, Loos C, et al. Distinct Early Serological Signatures Track with SARS-CoV-2 Survival. Immunity. 2020; 53(3):524-532. e4. doi: 10.1016/j.immuni.2020.07.020

43. Robbiani DF, Gaebler C, Muecksch F, Lorenzi JCC, Wang Z, Cho A, et al. Convergent antibody responses to SARS-CoV-2 in convalescent individuals. Nature. 2020; 584(7821):437-42. doi: 10.1038/s41586-020-2456-9

44. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229):1054-1062. doi: 10.1016/S0140-6736(20)30566-3

45. Lee WT, Girardin RC, Dupuis AP, Kulas KE, Payne AF, Wong SJ, et al. Neutralizing Antibody Responses to SARS-CoV-2 in COVID-19 Convalescent Sera. J Infect Dis. 2021;223(1):47-55. doi: 10.1093/infdis/jiaa673.

46. Levin AT, Hanage WP, Owusu-Boaitey N, Cochran KB, Walsh SP, Meyerowitz-Katz G. Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. Eur J Epidemiol. 2020;35(12):1123-38. doi: 10.1007/s10654-020-00698-1

47. Chandrashekar A, Liu J, Martinot AJ, McMahan K, Mercado NB, Peter L, et al. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. Science. 2020; 369(6505):812-817. doi: 10.1126/science.abc4776

48. Sadarangani M, Marchant A, Kollmann TR. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. Nat Rev Immunol. 2021;21(8):475-484. doi: 10.1038/s41577-021-00578-z

49. Mercado NB, Zahn R, Wegmann F, Loos C, Chandrashekar A, Yu J, et al. Single-shot Ad26 vaccine
protects against SARS-CoV-2 in rhesus macaques. Nature. 2020;586(7830):583-88. doi: 10.1038/s41586-020-2607-z

50. Chakraborty S, Gonzalez J, Edwards K, Mallajosyula V, Buzzanco AS, Sherwood R, et al. Proinflammatory IgG Fc structures in patients with severe COVID-19. Nat Immunol. 2021;22(1):67-73. doi: 10.1038/s41591-020-00828-7

51. Larsen MD, de Graaf EL, Sonneveld ME, Plomp HR, Nouta J, Hoepel W, et al. IgG characterizes enveloped viral responses and correlates with COVID-19 severity. Science. 2021;371(6532):eabc8378. doi: 10.1126/science.abc8378

52. Azkur AK, Akdis M, Azkur D, Sokolowska M, van de Veen W, Brüggen MC, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy. 2020;75(7):1564-1581. doi: 10.1111/all.14364

53. Behrens EM, Koretzky GA. Review: Cytokine Storm Syndrome: Looking Toward the Precision Medicine Era. Arthritis Rheumatol. 2017;69(6):1135-1143. doi: 10.1002/art.40071

54. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. Semin Immunopathol. 2017;39(5):517-528. doi: 10.1007/s00281-017-0639-8

55. Butler SE, Crowley AR, Natarajan H, Xu S, Weiner JA, Bobak CA, et al. Distinct Features and Functions of Systemic and Mucosal Humoral Immunity Among SARS-CoV-2 Convalescent Individuals. Front Immunol. 2021;11:618685. doi: 10.3389/fimmu.2020.618685

56. DiLillo DJ, Tan GS, Palese P, Ravetch JV. Broadly neutralizing hemagglutinin stalk-specific antibodies require FeγR interactions for protection against influenza virus in vivo. Nat Med. 2014;20(2):143-51. doi: 10.1038/nm.3443

57. Excler JL, Ake J, Robb ML, Kim JH, Plotkin SA. Non neutralizing functional antibodies: a new “old” paradigm for HIV vaccines. Clin Vaccine Immunol. 2014;21(8):1023-36. doi: 10.1128/CVI.00230-14

58. Liao M, Liu Y, Yuan J, Wen Y, Xu G, Zhao J, et al. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. Nat Med. 2020;26(6):842-44. doi: 10.1038/s41591-020-0901-9

59. Wen W, Su W, Tang H, Le W, Zhang X, Zheng Y, et al. Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. Cell Discov. 2020;6:31. doi: 10.1038/s41421-020-0168-9

60. Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, et al. Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. Cell. 2020;181(7):1489-1501.e15. doi: 10.1016/j.cell.2020.05.015

61. Peng Y, Mentzer AJ, Liu G, Yao X, Yin Z, Dong D, et al. Broad, and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19. Nat Immunol. 2020;21(11):1336-45. doi: 10.1038/s41591-020-0782-6

62. Needleman J, Luo X, Frouard J, Xie G, Gill G, Stein ES, et al. SARS-CoV-2-Specific T Cells Exhibit Phenotypic Features of Helper Function, Lack of Terminal Differentiation, and High Proliferation Potential. Cell Rep Med. 2020;1(6):100081. doi: 10.1016/j.xcrn.2020.100081

63. Ni L, Ye F, Cheng ML, Feng Y, Deng YQ, Zhao H, et al. Detection of SARS-CoV-2-Specific Humoral and Cellular Immunity in COVID-19 Convalescent Individuals. Immunity. 2020;52(6):971-77.e3. doi: 10.1016/j.immuni.2020.04.023

64. Weiskopf D, Schmitz KS, Raadsen MP, Grifoni A, Okba NMA, Endeman H, et al. Phenotype and kinetics of SARS-CoV-2-specific T cells COVID-19 patients with acute respiratory distress syndrome. Sci Immunol. 2020;5(48):eabd2071. doi: 10.1126/sciimmunol.abd2071

65. Wylie D, Mulchandani R, Jones HE, Philips ST, Brooks T, Charlett, Ades AE, et al. SARS-CoV-2 responsive T cell numbers are associated with protection COVID-19:a prospective cohort study in keyworkers. medRxiv (Preprint). 2020;20222778. doi: 10.11101/2020.11.02.20222778

66. Kuri-Cervantes L, Pampena MB, Meng W, Rosenfeld AM, Ittner CAG, Weisman AR, et al. Comprehensive mapping of immune perturbations associated with severe COVID-19. Sci Immunol. 2020;5(49):eabd7114. doi: 10.1126/sciimmunol.abd7114

67. Jeyanathan M, Afkhami S, Smaill F, Miller MS, Litchy BD, Xing Z. Immunological considerations for COVID-19 vaccine strategies. Nat Rev Immunol. 2020;20(10):615-32. doi: 10.1038/s41577-020-00434-6

68. Schultzje JL, Aschenbrenner AC. COVID-19 and the human innate immune system. Cell. 2021;184(7):1671-92. doi: 10.1016/j.cell.2021.02.029

69. Acharya D, Liu G, Gack MU. Dysregulation of type I interferon responses in COVID-19. Nat Rev Immunol. 2020;20(7):397-98. doi: 10.1038/s41577-020-0346-x

70. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Møller R, et al. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. Cell. 2020;181(5):1036-1045.e9. doi: 10.1016/j.cell.2020.04.026

71. Sa Ribero M, Jouvenet N, Dreux M, Nisole S. Interplay between SARS-CoV-2 and the type I interferon response. PLoS Pathog. 2020;16(7):e1008737. doi: 10.1371/journal.ppat.1008737

72. Banerjee AK, Blanco MR, Bruce EA, Honson DD, Chen LM, Chow A, et al. SARS-CoV-2 Disrupts Splicing, Translation, and Protein Trafficking to Suppress Host Defenses. Cell. 2020;183(5):1325-39.e21. doi: 10.1016/j.cell.2020.10.004

73. Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier...
K, White KM, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature. 2020;583(7816):459-68. doi: 10.1038/s41586-020-2286-9
74. Xia H, Cao Z, Xie X, Zhang X, Chen JY, Wang H, et al. Evasion of Type I Interferon by SARS-CoV-2. Cell Rep. 2020;33(1):108234. doi: 10.1016/j.celrep.2020.108234
75. Konno Y, Kimura I, Uiri K, Fukushima M, Irie T, Koyanagi Y, et al. SARS-CoV-2 ORF3b Is A Potent Interferon Antagonist Whose Activity Is Increased by a Naturally Occurring Elongation Variant. Cell Rep. 2020;32(12):108185. doi: 10.1016/j.celrep.2020.108185
76. Lei X, Dong X, Ma R, Wang W, Xiao X, Tian Z, et al. Activation and evasion of type I interferon responses by SARS-CoV-2. Nat Commun. 2020;11(1):3810. doi: 10.1038/s41467-020-17665-9
77. Ahmed-Hassan H, Sisson B, Shukla RK, Wijewantha Y, Funderburg NT, Li Z, et al. Innate Immune Responses to Highly Pathogenic Coronaviruses and Other Significant Respiratory Viral Infections. Front Immunol. 2020;11:1979. doi: 10.3389/fimmu.2020.01979
78. Park A, Iwasaki A. Type I and Type III Interferons - Induction, Signaling, Evasion, and Application to Combat COVID-19. Cell Host Microbe. 2020;27(6):870-78. doi: 10.1016/j.chom.2020.05.008
79. 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):403-416. doi: 10.1056/NEJMoa2035389
80. 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. doi: 10.1056/NEJMoa2034577
81. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomized controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99-111. doi: 10.1016/S0140-6736(20)32661-1
82. Logunov DY, Dolzhikova IV, Scheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzhharullaeva AS, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomized controlled phase 3 trial in Russia. Lancet. 2021;397(10275):671-681. doi: 10.1016/S0140-6736(21)00234-8
83. Widge AT, Rouphael NG, Jackson LA, Anderson EJ, Roberts PC, Makhene M, et al. Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. N Engl J Med. 2021;384(1):80-82. doi: 10.1056/NEJMct2032195
84. Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, et al. COVID-19 vaccine BNT162b1 elicits human antibody and T_{H}1 T cell responses. Nature. 2020;586(7830):594-99. doi: 10.1038/s41586-020-2814-7
85. Teijaro JR, Farber DL. COVID-19 vaccines: modes of immune activation and future challenges. Nat Rev Immunol. 2021;21(4):195-97. doi: 10.1038/s41577-021-00526-x.
86. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. Nat Rev Drug Discov. 2018;17(4):261-279. doi: 10.1038/nrd.2017.243
87. Wang Y, Zhang Z, Luo J, Han X, Wei Y, Wei X. mRNA vaccine: a potential therapeutic strategy. Mol Cancer. 2021;20(1):33. doi: 10.1186/s12943-021-01311-z
88. Eisenbarth SC. Dendritic cell subsets in T cell programming: location dictates function. Nat Rev Immunol. 2019;19(2):89-103. doi: 10.1038/s41577-018-0088-1
89. Ding Y, Guo Z, Liu Y, Li X, Zhang Q, Xu X, et al. The lectin Siglec-G inhibits dendritic cell cross-presentation by impairing MHC class I-peptide complex formation. Nat Immunol. 2016;17(10):1167-75. doi: 10.1038/ni.3535
90. Qiao J, Liu Z, Dong C, Luan Y, Zhang A, Moore C, et al. Targeting Tumors with IL-10 Prevents Dendritic Cell-Mediated CD8+ T Cell Apoptosis. Cancer Cell. 2019;35(6):901-15.e4. doi: 10.1016/j.ccell.2019.05.005
91. Dai L, Gao GF. Viral targets for vaccines against COVID-19. Nat Rev Immunol. 2021;21(2):73-82. doi: 10.1038/s41577-020-00480-0
92. Röthgen K, Nielsen SCA, Arunachalam PS, Yang F, Hoh RA, Wirz OF, et al. mRNA vaccination compared to infection elicits an IgG-predominant response with greater SARS-CoV-2 specificity and similar decrease in variant spike recognition. medRxiv [Preprint]. 2021:2021.04.05.21254952. doi: 10.1101/2021.04.05.21254952
93. Sayedahmedd EE, Elkashif A, Alhashimi M, Sambharo S, Mittal SK. Adenoviral Vector-Based Vaccine Platforms for Developing the Next Generation of Influenza Vaccines. Vaccines (Basel). 2020;8(4):574. doi: 10.3390/vaccines8040574
94. Pritchard E, Matthews PC, Stoesser N, Eyre DW, Gethings O, Vihta KD, et al. Impact of vaccination on new SARS-CoV-2 infections in the United Kingdom. Nat Med. 2021 . doi: 10.1038/s41591-021-01410-w