MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Virology & Immunology Journal
ISSN: 2577-4379

How Will the Covid-19 Vaccines Help Shape the Herd Immunity against Covid-19?

Addison A, Parker A, Dixon L and Weitao T*

Natural Sciences, Geneva Casebolt College of Arts & Sciences, Southwest Baptist University, USA

***Corresponding author:** Tao Weitao, Geneva Casebolt College of Arts & Sciences, Southwest Baptist University; 1600 University Avenue. Bolivar, Missouri 65613, USA, Tel: 4173281470; Email: twei@sbuniv.edu

Editorial

Volume 5 Issue 1

Received Date: December 26, 2020

Published Date: January 21, 2021

DOI: 10.23880/vij-16000264

Abstract

Severe acute respiratory coronavirus-2 (SARS-CoV-2 and the related disease COVID-19) has revealed the devastating impact of the pandemic on a susceptible human population. Herd immunity is considered as an effective intervention to restrict the viral spread based on the conception that the proportion of individuals immune to SARS-CoV-2 is greater than the herd immunity threshold at which persistent transmission is unlikely to occur so that the pandemic is likely to decline. Herd immunity threshold varies with environmental, epidemiological and immunological settings. Establishment of herd immunity against SARS-CoV-2 within a population can be achieved by two approaches. The first is a large scale of vaccination that demands a safe and effective vaccine. The principles of vaccination against COVID-19 stem from cross-reactive immunity based on evidence from the pre-existing cross-reactive immune memory to SARS-CoV-2 that primarily originates from previous exposure to common cold coronaviruses circulating in the human population. The second is natural recurrent infections, the consequences of which are more serious and far-reaching at the cost of infection of a large proportion of the human population and death of the susceptible people. In the absence of the vaccines, many countries have implemented social distancing mandates and quarantine strategies to limit transmission and lower the infection rate; but another solution is effective vaccination, both of which facilitate herd immunity. A COVID-19 vaccine BNT162b1 has been developed, which is a lipid nanoparticle-formulated nucleoside-modified mRNA coding for the receptor-binding domain of the spike protein on the SARS-CoV-2 virion. The phases I/II trial data indicate that the vaccine is safe with mild side effects and induces both antibody and T cell responses, making it promising for phase III trial. Conclusions from the preliminary phase III data demonstrate efficacy of this candidate. Here we intend to provide insights about the role of vaccination in development of herd immunity and perspectives of the mRNA-based vaccine candidate in the context of pandemics.

Keywords: COVID-19; Severe Acute Respiratory Coronavirus; Herd Immunity; Vaccine; Infection; Clinical Trial

Introduction

With the threat of millions of lives at stake and the critical timeline to return to normalcy, the world has been racing for a vaccine to alleviate the spread of severe acute respiratory coronavirus-2 (SARS-CoV2). The related disease COVID-19 is highly complex with distinct pathology. Previous studies on MERS and SARS have proved to be helpful by providing a better understanding of COVID-19. However, despite the similarities between MERS and SARS, COVID-19 has been difficult to treat successfully. Multiple countries have implemented social distancing mandates and quarantine strategies to limit the transmission of the disease and lower the infection rate. While these tactics have helped lower the spread of the infection, they do not serve as a cure for a worldwide crisis. An effective vaccination with the goal of herd immunity is the solution to stop this pandemic. The

need for a safe and effective vaccine is imperative.

The emergence of a novel virus SARS-CoV-2 and the resulting disease COVID-19 has revealed the devastating impact of the emerging viral pathogen on a susceptible human population. As a result, the idea of individual immunity has become somewhat familiar to the public. Many of us understand that when exposed to such an infective agent as SARS-CoV2, a person's body is able to identify the agent as harmful and to mount a defense against it. However, what happens when a group of individuals is exposed to a pathogen can be harder to conceptualize, as members in the group introduce new variables to the equation of pathogen versus host ($p_I = 1 - 1/R_0$ where p_I is the fraction of immune individuals, and R_0 the reproduction number of a pathogen in the absence of intervention in a susceptible population). Herd immunity against COVID-19, then, could be thought of as the interaction between SARS-CoV-2 and the exposed human population as discussed recently [1]. When approached from this perspective, we can see that the characteristics of a pathogen such as SARS-CoV-2 in a given human population can change the dynamics of herd immunity [2]. Herd immunity is considered to be achieved through either naturally acquired infections or artificially acquired vaccinations once the herd immunity threshold p_I is less than 1. This means that one infected person infects less than one other person [3]. Once this threshold is reached, people who do not have the protective immunity to the pathogen are protected since the pathogen runs out of susceptible hosts and is unable to spread throughout a population. The efficacy of herd immunity mainly hinges on strength and duration of the acquired protective immunity as reviewed recently [2]. This is an important concept to keep in mind when applying the concept of herd immunity to a novel disease, such as COVID-19. While the long-term immune response to SARS-CoV-2 is not fully understood, we intend to provide insights about the role of vaccination in development of herd immunity.

Factors Affecting Herd Immunity

Herd immunity is developed after one infected individual in a certain human population makes less than one secondary case averagely, a scenario well documented recently [1]. It is dependent on the effective reproduction number R that is defined as the average number of people infected by a single case. When people mix homogeneously so that they are equally susceptible and infectious in a population, $R = (1 - p_C)(1 - p_I) R_0$ (p_C, the relative decrease in transmission rates under non-pharmaceutical interventions such as social distancing and wearing facial masks; p_I, the fraction of immune persons; and R_0, the reproduction number for a certain pathogen circulated in a fully susceptible population in the absence of intervention). In the absence of pharmaceutical intervention, $p_C = 0$ to reach $R = (1 - p_I) R_0$. For herd immunity to be achieved, $R < 1$ [$R \leq 1 = (1 - p_I) R_0$)] so that the fraction of immune persons or herd immunity threshold reaches $p_I = 1 - 1/R_0$. R_0 may vary across different kinds of pathogens, human populations and epidemic periods, and be subject to potentially environmental and epidemiological factors. While herd immunity development is affected by multiple factors, vaccination is essential. Epidemiological factors that have significant implications in the setting of herd immunity as reviewed recently [2] are difficult to determine due to the inadequate data. These factors include not only cultural behaviors, population density and age structure, but also underlying comorbidity and contact rates across groups. This fundamentally suggests that the herd immunity threshold also varies among the exposed human populations [4], in which communicability for any infectious disease relies on numerous factors that influence transmission dynamics, such as structure and density of human population and differences in contact rates across demographic groups [5]. These factors affect R_0 directly or indirectly, and subsequently, the herd immunity threshold. Since these factors influence transmission dynamics of community spread, assumptively uniform R_0 and p_I across populations appear unrealistic.

Herd immunity starts to form when the proportion of individuals immune to a certain pathogen is greater than the herd immunity threshold $p_I = 1 - 1/R_0$. This is when the herd immunity threshold is attained in a population so that persistent transmission is unlikely to occur and the outbreak is likely to decline. In $1 - 1/R_0$, R_0 is the basic reproduction number dependent on both the type of the pathogen and the features of the infected human population as discussed above. A single pathogen can have various R_0 values that are determined by the features and transmission dynamics of the exposed human population [4]. For example, if $R_0 = 3$ in ($p_I = 1 - 1/R_0$) for SARS-CoV-2, the herd immunity threshold p_I is 67% (1-1/3), suggesting that decline of the infection incidence will not start until 67% of the population acquire immunity against SARS-CoV-2. It is also predicted from $R = (1 - p_C)(1 - p_I)R_0$ that in the advent of herd immunity, the degree of social distancing measures of non-pharmaceutical interventions are still required to control transmission (p_C) as population immunity (p_I) increases. Indeed, the transmission rates (p_C) must decrease by 67% if the population is entirely susceptible, and by 43% if 43% of the population acquires immunity (p_I) so that R <1 meaning that one case can infect less than one person. Noticeably, with the promising vaccination in progress, the social distancing and wearing masks measure should still be followed to maintain the herd immunity effectively.

As for the immunological factors for COVID-19 herd immunity, the development of the anti-viral herd immunity

hinges on whether the natural infection induces the adequate protective immunity. Reinfection of SARS-CoV-2 in a small cohort of rhesus macaques could not occur until one month post the initial viral challenge, the result suggestive of at least short-term protective immunity in the animal model [6]. Moreover, serum neutralizing antibodies specific for SARS-CoV-2 were present in a cohort of most of 175 recovered COVID-19 patients [7], demonstrating the presence of SARS-CoV-2 neutralizing antibodies in humans. Furthermore, the neutralizing antibody responses against SARS-CoV persisted in the confirmed SARS patients from several months to two years [8]. The raised concentrations of antibodies specific to coronavirus 229E responsible for the common cold were detected one year after infection, but the titers were not adequate to prevent the individuals from reinfection [9]. The results from these studies suggest that protective immunity against reinfection with the coronavirus species last for a certain period. Annual outbreaks would result from short-term immunity of ~ten months, but biennial outbreaks from the longer-term immunity of ~two years as predicted from modeling of the SARS-CoV-2 transmission dynamics [10]. Although reinfection happens after waning of protective immunity, recurrent enhancement of the memory immune cells of the adaptive immunity, especially the T cell immunity through vaccination, is likely to maintain persistent herd immunity that prevents future pandemics. Altogether, the herd immunity in real-world populations is often affected by epidemiological and immunological factors. Such factors as waning of protective immunity as function of population structure and variation in dynamics of transmission between populations may vary the scope of indirect protection provided by herd immunity.

Vaccination Helps Shape Herd Immunity

Establishment of herd immunity against SARS-CoV-2 within a population can be achieved by two approaches. The first is a large scale of vaccination that demands a safe and effective vaccine. The second is natural recurrent infections, the consequences of which are more serious and far-reaching at the cost of infection of a large proportion of human population and death of the susceptible people. Although in the absence of vaccination, it is theoretically possible to develop COVID herd immunity through natural infections. Since there is no feasible, ethical path to accomplish this goal without the devastating societal consequences, the persistent herd immunity against SARS-CoV-2 are unrealistic without recurrent vaccination. An effective vaccine against COVID-19 is the safest path to achieve herd immunity as reviewed recently [1]. With six SARS-CoV-2 vaccines having reached phase III trials as of August 2020, effective vaccines are likely available later in 2021. Vaccination is the most appropriate method for generating herd immunity based on $R = (1 - p_C)\ (1 - p_I)\ R_0 \leq 1$. This is because during initial stage of the production and delivery of a vaccine, the highly exposed people and those at risk of severe morbidity can be prioritized for vaccination. The vaccination can specifically target the exposed populations of high risk, such as medical professionals, health-care workers or individuals with frequent contact with patients and customers. Fatalities can be minimized by vaccinating the highly susceptible people. Moreover, vaccination may reduce viral circulation (R_0) in the exposed population more efficiently than the naturally acquired immunity, especially when the naturally acquired protective immunity needs boosts over re-infections. For vaccination, vaccines can be boosted routinely. All these measures can reduce viral reproduction R_0 but increase human population immunity p_I to help reach $R = (1 - p_C)\ (1-p_I)R_0 \leq 1$. Altogether, effective vaccination facilitates formation of herd immunity against COVID-19.

Vaccination is Based On Cross-Reactive Immunity

Immunity is a multifaceted function, from which immunological considerations for COVID-19 vaccine strategies have been reviewed recently [11]. The principles of vaccination against COVID-19 stem from cross-reactive immunity based on evidence from the pre-existing cross-reactive immune memory to SARS-CoV-2 that chiefly originates from previous exposure to common cold coronaviruses circulating in the human population as discussed recently [12]. Pre-existing cross-reactive immunity against COVID-19 exists in humans. In a study involving 35% of healthy individuals who were not exposed to SARS-CoV-2, their $CD4^+$ T cells recognized the S protein of SARS-CoV-2; additionally, in 40–60% of the unexposed persons, the $CD4^+$ T cells reacted with the non-S proteins of SARS-CoV-2 [13,14]. These results demonstrate the presence of cross-reactivity of $CD4^+$ T cells with the specificity between SARS-CoV-2 and other coronaviruses [15-18]. Among four human coronaviruses (229E, NL63, OC43 and HKU1) responsible for approximately 15% of common colds in humans [11], one of them infected adults every 2–3 years averagely, suggesting a certain level of pre-existing cross-reactive immunity to SARS-CoV-2 antigens in these groups. Such pre-existing cross-reactive immunity may contribute to various protection and susceptibility to SARS-CoV-2 infection. Furthermore, both S1 and S2 subunits of SARS-CoV-2 are equally recognized by the $CD4^+$ T cells from patients with COVID-19, while the S2 subunit is recognized by the cross-reactive $CD4^+$ T cells from unexposed people [14]. From patients with COVID-19, the $CD4^+$ T cells cross-react intensely with S2 subunits of the human coronavirus strains OC43 and 229E. Although over 90% of the tested healthy adults have IgG antibodies specific for all four human common cold coronaviruses [15], the

humoral responses to human coronaviruses are short-lived for months after infection. Hence, reinfection with human coronaviruses appears to be controlled mainly by T cell immunity [15]. The evidence of the cross-immunity between the pre-existing immunity against human coronaviruses and the protective immunity against SARS-CoV-2 gives confidence in the development of the COVID-19 vaccine-induced protective immunity via the vaccine-boosted cross-reactive immune responses.

A Novel COVID-19 Vaccine

There are four main structural proteins of the SARS-CoV-2 virion: nucleocapsid (N) protein, envelope (E) protein, matrix (M) protein and spike (S) protein. N protein assists RNA synthesis as it coats the positive-stranded RNA genome. E and M proteins help with viral assembly and are located inside a lipid viral envelope. Among these proteins, S protein is the common target for SARS-CoV-2 vaccinations since it can induce immune responses. COVID-19 vaccine BNT162b1 is a lipid nanoparticle-formulated nucleoside-modified mRNA coding for the receptor-binding domain (RBD) of the S protein on the SARS-CoV-2 virion, which is a crucial target of the neutralizing antibodies. In an effort to enhance the immunogenicity of the vaccine by multivalent display, a phage T4 fibritin-derived 'foldon' trimerization domain is fused with RBD expressed by the BNT162b1 mRNA [19]. The BNT162b1 mRNA to be translated into the protein antigens by the host cells is optimized for translation efficiency with high stability [20,21]. To reduce innate immune sensing and to increase translation of the mRNA vaccine in vivo, 1-methylpseudouridine is incorporated instead of uridine [22]. Once the vaccine mRNA enters the host cells, it is translated transiently but not integrated into the host genome. Before the use on the biological systems, the mRNA vaccine is synthesized through a cell-free transcription process from DNA in vitro, so it is free from ingredients of any animal origin [23-25].

With this COVID-19 RNA vaccine BNT162b1, current placebo-controlled, observer-blinded phase I/II clinical trials were conducted in adults. The results demonstrate not only safety and tolerability of this vaccine but also the robust antibody response from the vaccination [26]. The data from the subsequent, non-randomized open-label phase I/II trial conducted in healthy adults aged 18-55 of years indicate strong antibody and T cell responses after the BNT162b1 vaccination [27]. Both robust $CD4^+$/ $CD8^+$ T cell responses and antibody responses were elicited by two doses of BNT162b1. The RBD-recognizing IgG concentrations went beyond the levels in sera from a cohort of the COVID-19 convalescent people [27]. In some asymptomatic cases after SARS-CoV-2 exposure, the cellular immune response was detected without seroconversion; therefore, T cells specific for SARS-CoV-2 appear to play a main role in control of the infections even without the neutralizing antibodies [28]. Indeed, the long-lasting immune memory against coronavirus infections depends on $CD4^+$ and $CD8^+$ T cells as demonstrated by $CD8^+$ T cells that persisted in SARS-CoV-1 survivors for 6–11 years. Specifically, the induced cellular immunity includes T helper type 1 (T_H1)-skewed T cell responses together with expansion of RBD-specific $CD8^+$ and $CD4^+$ T cells, both of which mostly produced interferon-γ. IFNγ, a cytokine for multiple antiviral responses, is involved in a coordinated immune response against a viral intrusion [29]; in fact, it inhibits SARS-CoV replication in synergy with type I interferons [30]. People with the genetically impaired-IFNγ activity are highly susceptible to SARS [31]. Therefore, the BNT162b1 mRNA vaccine induces the robust responses of RBD-specific antibodies and CD4/8 T cells with antiviral cytokines, such as IFNγ, suggesting multiple defense mechanisms against COVID-19 [27].

What Clinical Trials are Revealing about COVID-19 Vaccination?

The race to developing a vaccine against COVID-19 has been an unprecedented medical effort. As the production of new vaccines traditionally takes between five and ten years of vaccine trials, remarkable progress has been made in vaccine development during the nine months COVID-19 has been declared a pandemic. Vaccine trials go through various phases of development to ensure their safety and effectiveness. In the preclinical phase, scientists study the chemical makeup of the vaccine candidate and determine if it induces immune responses and how it interacts in living organisms; animal studies are included in this phase. If immunogenic, it goes through phase I where researchers test human volunteers over a placebo and the vaccine candidate respectively to assess its safety and side effects. In phase II, participants are tested to determine immunogenicity and correct dosages of the vaccine candidate and the related short-term effects. Phase III clinical trials move on to a larger population not only to confirm the vaccine's safety and effectiveness but also to prove the vaccine-induced protection of the participants from the natural infections.

The mRNA-based vaccine candidates have been gone through the phase I and II trials. In preclinical COVID-19 vaccination trials in mice, a vaccine called RQ3013-VLP was effective at triggering an immune response [32]. This vaccine works by introducing mRNA that encodes proteins associated with coronavirus such as virus like particles (VLPs). A booster injection significantly increased antibody titer and proved stable after week 8. No adverse effects were observed after vaccination. RQ3013-VLP elicited both humoral and cellular responses, making it a strong candidate for future research. Additionally, a phase I/II study

of COVID-19 RNA vaccine BNT162b1 was performed in human adults. The vaccine candidate is a lipid-nanoparticle-formulated, nucleoside-modified mRNA vaccine encoding the trimerized RBD of the SARS-CoV-2 S protein. The vaccine was inoculated into the randomized 45 healthy adults aged 18-55 years in two doses-separated by 21 days in an ongoing placebo-controlled, observer-blinded dose-escalation study. The data indicate that the vaccine is safe, tolerate, and immunogenic with dose-dependent local reactions and mild systemic events [26]. BNT162b1 was further tested in human clinical trials as discussed above [27]. The robust T cell and antibody responses were found (27) although limited success was found with the vaccine candidate that target RBD in the mouse trials [32]. This response was found to be higher than was observed in the serum of those recovered from COVID-19, suggesting that vaccination with BNT162b1 could increase immunity even for these individuals. Side effects associated with the vaccine were dose-dependent including headache, chills, fatigue, and muscle pain [27]. Another vaccine candidate mRNA-1273 was tested in 40 elderly adults (56+ years of age) [33]. The vaccine mRNA encodes the SARS-CoV-2 spike protein, which triggers a CD4 cytokine response facilitated by type 1 helper T cells. The immune response of the older group was similar to a previous study that had tested younger individuals (18-55 years of age). The side effects, similar to the younger group, were dose-dependent and more prevalent after the second dose. Lastly, results from an interesting study show that children may be partially protected from COVID-19 due to cross-reactive immunity from diphtheria, tetanus, and pertussis (DTP) vaccinations [34]. Since B and T cells recognize small fragments within antigens called epitopes, antigen peptide sequences match those of SARS-CoV-2 for possible sources of cross-reactive immunity. If childhood DTP vaccinations confer cross-reactive immunity against COVID-19, it would explain why the vast majority of victims are elderly (over the age of 70) since immunity from DTP vaccines wane over time. Taken together, the data from phases I/II indicate that the mRNA-based vaccine candidates, which are safe with mild side effects, induce both antibody and T cell responses, making them promising candidates for the phase III trials.

Conclusion

Perspectives

Several vaccine candidates including Pfizer-BioNTech, Moderna, AstraZeneca, Janssen COVID-19 vaccines are in the Phase III clinical trials [35]. The Phase III trial of BNT162b2 developed by Pfizer and BioNTech has been in progress since July 27 of 2020 [36]. The participants that have racially and ethnically diverse backgrounds have been enrolled from numerous clinical trials sites in United States and several other countries in Europe, Africa, America, and Asia. The age ranges from 56 to 85 years of approximately 41% of global and 45% of U.S. participant. Of 43,661 participants enrolled, 94% (41,135) have received a second dose of BNT162b2 as of November 13 of 2020. The results of the final efficacy analysis based on a fraction of the participants enrolled in this continuing Phase III trial demonstrate that BNT162b2 satisfies all the primary efficacy endpoints. The first primary objective was met as a vaccine efficacy rate reached 95% ($p<0.0001$) in the group of the participants without prior COVID-19, while the second primary objective was also achieved in the group both with and without prior COVID-19. Each case was measured from 7 days after the second dose. In particular, of 170 cases of COVID-19 defined in the study protocol, 95% (162 infected cases) of COVID-19 were observed in the placebo group with 5% uninfected, whereas 5% (8 cases) infected were seen in the BNT162b2 group with 95% uninfected as indicated from the first primary objective analysis. The efficacy was > 94% in adults over 65 years of age. There was consistency of the efficacy from this preliminary study across age, gender, race and ethnicity demographics. Additionally, the safety requirement of BNT162b2 by the U.S. Food and Drug Administration (FDA) for Emergency Use Authorization (EUA) has been satisfied. EUA for both Pfizer-BioNTech and Moderna COVID-19 Vaccines (mRNA based) have been authorized recently [37,38]. Mass vaccine production is expected by the end of 2021. The efficacy and safety data in participants will be collected continuously from the ongoing trial for an additional two years.

In each of these studies, we see the need for larger sample sizes in order to compile more accurate data about COVID-19 vaccination. As more vaccines are approved to move on to phase III clinical trials, we expect to learn more about the implications of each vaccine through larger sample sizes and become informed on the best decision to move forward with. Another commonality in these studies highlights the importance of a booster shot to maintain the presence of antibodies and T cells in the body to target the viral pathogen. Without a second round of vaccination, the immune responses were not found to be very effective against the infection in any of the above trials, even in relatively high doses. However, booster shots significantly increased titer levels of antibodies in a dose-dependent fashion. Side effects were also observed to be dose-dependent, with higher doses of vaccination more likely to produce mild to moderate adverse effects that were consistent across various trials, with no serious complications on record. So far, the COVID-19 vaccinations in the clinical trials have proved to be safe and have produced promising immune responses against SARS-CoV-2. These results give hope to the public who have been long awaiting an answer to build up and maintain the herd immunity against the spreading pandemic.

Acknowledgements

We thank Division of Natural Sciences, Geneva Casebolt College of Arts & Sciences, and Southwest Baptist University for funding support.

References

1. Fontanet A, Cauchemez S (2020) COVID-19 herd immunity: where are we?. Nature Reviews Immunology 20(10): 583-584.

2. Randolph HE, Barreiro LB (2020) Herd Immunity: Understanding COVID-19. Immunity 52(5): 737-741.

3. Ledford H, Cyranoski D, Van Noorden R (2020) The UK has approved a COVID vaccine - here's what scientists now want to know. Nature 588: 205-206.

4. Delamater PL, Street EJ, Leslie TF, Yang YT, Jacobsen KH (2019) Complexity of the Basic Reproduction Number (R(0)). Emerging infectious diseases 25: 1-4.

5. Anderson RM, May RM (1985) Vaccination and herd immunity to infectious diseases. Nature 318(6044): 323-329.

6. Bao L, Deng W, Gao H, Xiao C, Liu J, et al. (2020) Reinfection could not occur in SARS-CoV-2 infected rhesus macaques. bioRxiv.

7. Wu F, Wang A, Liu M, Wang Q, Chen J, et al. (2020) Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. medRxiv.

8. Mo H, Zeng G, Ren X, Li H, Ke C, et al. (2006) Longitudinal profile of antibodies against SARS-coronavirus in SARS patients and their clinical significance. Respirology 11(1): 49-53.

9. Callow KA, Parry HF, Sergeant M, Tyrrell DAJ (2009) The time course of the immune response to experimental coronavirus infection of man. Epidemiology and Infection 105(2): 435-446.

10. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M (2020) Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. Science 368: 860-868.

11. Jeyanathan M, Afkhami S, Smaill F, Miller MS, Lichty BD, et al. (2020) Immunological considerations for COVID-19 vaccine strategies. Nature Reviews Immunology 20: 615-632.

12. Lipsitch M, Grad YH, Sette A, Crotty S (2020) Cross-reactive memory T cells and herd immunity to SARS-CoV-2. Nature Reviews Immunology 20: 709-713.

13. Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, et al. (2020) Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. Cell 181(7) 1489-1501.e1415.

14. Braun J, Loyal L, Frentsch M, Wendisch D, Georg P, et al. (2020) SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. Nature 587: 270-274.

15. Sariol A, Perlman S (2020) Lessons for COVID-19 Immunity from Other Coronavirus Infections. Immunity 53: 248-263.

16. Ahmed SF, Quadeer AA, McKay MR (2020) Preliminary Identification of Potential Vaccine Targets for the COVID-19 Coronavirus (SARS-CoV-2) Based on SARS-CoV Immunological Studies. Viruses (1999-4915) 12(3): 254.

17. Mateus J, Grifoni A, Tarke A, Sidney J, Ramirez SI, et al. (2020) Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans. Science 370: 89-94.

18. Le Bert N, Tan AT, Kunasegaran K, Tham CYL, Hafezi M, et al. (2020) SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. Nature 584(7821): 457-462.

19. Tai W, Zhao G, Sun S, Guo Y, Wang Y, et al. (2016) A recombinant receptor-binding domain of MERS-CoV in trimeric form protects human dipeptidyl peptidase 4 (hDPP4) transgenic mice from MERS-CoV infection. Virology 499: 375-382.

20. Holtkamp S, Kreiter S, Selmi A, Simon P, Koslowski M, et al. (2006) Modification of antigen-encoding RNA increases stability, translational efficacy, and T-cell stimulatory capacity of dendritic cells. Blood 108: 4009-4017.

21. Orlandini von Niessen AG, Poleganov MA, Rechner C, Plaschke A, Kranz LM, et al. (2019) Improving mRNA-Based Therapeutic Gene Delivery by Expression-Augmenting 3′ UTRs Identified by Cellular Library Screening. Molecular Therapy 27(4): 824-836.

22. Karikó K, Muramatsu H, Welsh FA, Ludwig J, Kato H, et al. (2008) Incorporation of Pseudouridine Into mRNA Yields Superior Nonimmunogenic Vector With Increased Translational Capacity and Biological Stability. Molecular Therapy 16(11): 1833-1840.

23. Sahin U, Karikó K, Türeci Ö (2014) mRNA-based therapeutics — developing a new class of drugs. Nature

Reviews Drug Discovery 13: 759-780.

24. Rauch S, Jasny E, Schmidt KE, Petsch B (2018) New Vaccine Technologies to Combat Outbreak Situations. Frontiers in Immunology 9: 1963.

25. Pardi N, Tuyishime S, Muramatsu H, Kariko K, et al. (2015) Expression kinetics of nucleoside-modified mRNA delivered in lipid nanoparticles to mice by various routes. Journal of Controlled Release 217: 345-351.

26. Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, et al. (2020) Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature 586: 589-593.

27. Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, et al. (2020) COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature 586: 594-599.

28. Gallais F, Velay A, Nazon C, Wendling MJ, Partisani M, et al. (2021) Intrafamilial Exposure to SARS-CoV-2 Associated with Cellular Immune Response without Seroconversion, France. Emerg Infect Dis 27.

29. Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, et al. (2020) Immunology of COVID-19: Current State of the Science. Immunity 52(6): 910-941.

30. Sainz B, Mossel EC, Peters CJ, Garry RF (2004) Interferon-beta and interferon-gamma synergistically inhibit the replication of severe acute respiratory syndrome-associated coronavirus (SARS-CoV). Virology 329: 11-17.

31. Chong WP, IP WKE, Tso GHW, Ng MW, Wong WHS, et al. (2006) The interferon gamma gene polymorphism +874 A/T is associated with severe acute respiratory syndrome. BMC Infectious Diseases 6: 82.

32. Lu J, Lu G, Tan S, Xia J, Xiong H, et al. (2020) A COVID-19 mRNA vaccine encoding SARS-CoV-2 virus-like particles induces a strong antiviral-like immune response in mice. Cell Research 30: 936-939.

33. Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, et al. (2020) Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. N Engl J Med 383: 2427-2438.

34. Reche PA (2020) Potential Cross-Reactive Immunity to SARS-CoV-2 From Common Human Pathogens and Vaccines. Front Immunol 11: 586984.

35. CDC (2020) Different COVID-19 Vaccines.

36. Bio NTech Pa (2020) Pfizer and BioNTech Conclude Phase 3 Study of COVID-19 Vaccine.

37. FDA (2020) Pfizer-BioNTech COVID-19 Vaccine Authorized for Emergency Use.

38. FDA (2020) Moderna COVID-19 Vaccine Authorized for Emergency Use.