THE NEW ARMENIAN MEDICAL JOURNAL
Vol.16 (2022), No 1 p. 4-12
DOI: https://doi.org/10.56936/18290825-2022.16.1-4

RECOMMENDED TACTICS FOR MASS VACCINATION OF HEALTHY INDIVIDUALS AND COVID-19 CONVALESCENTS

Zilfyan A.V.[1], Avagyan S.A.[1], Muradyan A.A.[2], Barsegyan E.S.[3]

[1] Scientific-Research Center, Yerevan State Medical University, Yerevan, Armenia
[2] Rector of Yerevan State Medical University Yerevan, Armenia
[3] Head of Mikaelyan Institute of Surgery, Yerevan, Armenia

Received 21.08.2021; accepted for printing 18.01.2022

Abstract

This article presents our views on main scientific and methodological approaches regarding the advantages of conducting mass vaccination of healthy individuals and COVID-19 convalescents.

First of all, the focus is on issues regarding the antigenic potencies of SARS-CoV-2, based on which vaccines have been created over the past three years that have successfully passed preclinical and clinical testing, as well as licensing. The subjects of specal discussion were aspects related to the short-term effect of the main vaccines, as a result of which revaccination is recommended. It is assumed that more than one antigenic determinant is expressed on the surface of SARS-CoV-2.

In the conclusion paragraph, we have presented our own concept on most topical situational issues among the population of many countries in the process of vaccination against COVID-19.

1. *Is it worth getting vaccinated at all if complications can arise that lead to disability and death even in practically healthy individuals, not to mention the elderly contingent with chronic diseases?*
2. *In making a positive decision, the question arises in terms of choosing a vaccine, since vaccines are used in different countries, in the production of which different scientific, methodological and technological approaches are used.*
3. *If there is a need for re-vaccination within a short period after the first vaccination?*
4. *As a rule, it is recommended to re-vaccinate in 14-30 days after the first vaccination. In this regard, there are concerns about the low efficacy (weak selective immunogenic activity) of vaccines.*
5. *How expedient, if not contraindicated, is to "fully" vaccinate patients in the recovery period, as well as over the next one to two months, if they have high levels of SARS-CoV-2 antibodies?*
6. *In case of re-vaccination, it is necessary to find out whether it is possible to get the second vaccination using a commercial vaccine of another manufacturer, especially since many developing countries do not currently have such a vaccine that has been introduced during the first vaccination.*
7. *How competent is it to vaccinate a wide range of healthy individuals against COVID-19 and influenza - for the same time or with the shortest time interval?*

Keywords: *COVID-19, SARS-CoV-2, receptors, antigens, mass vaccination, convalescents.*

Despite deaths caused by coronavirus pandemic, healthy individuals in many countries of the world are very skeptical of the requirements of epidemiologists, virologists and infectious disease specialists to strictly adhere to the directives of the responsible authorities and their subordinate health authorities, according to which vaccination against SARS-CoV-2 should considered as a mandatory "humanitarian and health" campaign of international importance [*Pandey S et al., 2020; Poland G et al., 2020*].

Concerns about vaccination safety and risks arise due to a number of subjective and objective reasons associated with our incomplete knowledge of the mechanisms underlying coronavirus pneumonia and

Cite This Article as:

Zilfyan A.V., Avagyan S.A., Muradyan A.A., Barseghyan E.S. (2022); Recommended tactics for mass vaccination of healthy individuals and COVID-19 convalescents; NAMJ v.16 (2022) No.1, p. 4-12;
DOI: https://doi.org/10.56936/18290825-2022.16.1-4

Address for Correspondence:

Arto V Zilfyan
Scientific Research Center, Yerevan State Medical University after M. Heratsi, 2 Koryun Street, Yerevan 0025, Armenia
E-mail: namj.ysmu@gmail.com; Tel.: (+374 93) 58-86-97

"visceral" clinical and anatomical manifestations. Moreover, during COVID-19 treatment, the lungs are dominant study objects, meanwhile dystrophic and destructive processes developing in many organs and tissues also have a negative effect on the regional pathological process in lungs [*Chen T et al., 2020; Ferrari D et al., 2020; Guo T et al., 2020; Huang C et al., 2020; Soeiarto G, 2020; Shi S et al., 2020; Tang N et al., 2020; Zhou F et al., 2020; Avagyan S et al., 2021a; Chilingaryan T et al., 2021; Melik-Nubaryan D et al., 2021; Sisakyan A et al., 2021; Supit V et al., 2021; Zilfyan A et al., 2021*].

The situation is more complicated, since it is practically not "recommended" to open corpses. Due to the absence of a pathological diagnosis, based on clinical symptoms and routine laboratory tests, it is impossible to characterize the entire symptom complex of macroscopic and microscopic changes that occur in the body of COVID-19 patients.

In this regard, in our opinion, the subject of special discussion continues to be the hypothesis that there is a threat of developing "multiple organ dysfunction syndrome" during COVID-19 [*Devaux C et al., 2020*].

The hypothesis about the possible development of "multiple organ failure syndrome" involving a wide range of internal organs in the pathological process allows, in our opinion, to consider COVID-19 as a "systemic disease" since many "visceral" manifestations (which leave their impact on the character and the course of pneumonia), undoubtedly should be considered as independent criteria in the general symptom complex of coronavirus infection development [*Zilfyan A et al., 2021*]. So, the according to Sugihartono T. and co-authors (2020), depending on the severity of COVID-19 infectious process, the "intestine-lungs" axis begins to function, which is implemented on the principles of interaction and interdependence of pathological processes in both systems.

Researchers should follow the same scientific and methodological approach in relation to other integrative systems of the body, where COVID-19 causes severe dystrophic and destructive processes, in general, reflecting the entire symptom complex of systemic disorders.

This current situation has a very negative impact on finding effective remedies, most likely based not on the principles of symptomatic, but on pathogenetic therapy of COVID-19 patients. In this regard, the scientific and methodological approach that is selectively aimed at inhibiting polyamine-dependent processes responsible for persistence, transcription and replication of SARS-CoV-2 in an infected organism seems very reasonable. Unfortunately, there are vey few studies in this direction, and they have not found their proper assessment at present [*Avagyan S et al., 2020; 2021a; Zilfyan A et al., 2020; 2021*].

The situation from 2019 up to present (during COVID-19 pandemic), as well as the well-known-difficulties in searching effective treatment methods for coronavirus infection, were the basis for finding new immunoprophylactic approaches, mainly based on the mass vaccination of practically healthy individuals and COVID-19 convalescents..

Vaccination, as a way to effectively combat viral diseases, turned out to be promising even "at the dawn" of immunology development. As an illustrative example, it is enough to cite the smallpox vaccine introduced by E. Jenner in 1796; however, vaccination results exceeded all expectations. So, over the next two years after the introduction, 100,000 people were vaccinated with a high degree of effectiveness. Unfortunately, the introduction of the smallpox vaccine over the next few years did not lead to the further immunology development of infectious diseases, since many approaches associated with the creation and testing of effective vaccines very often turned out to be ineffective. As "typical" examples, it suffices to point out the relatively low efficacy of vaccines used for influenza and HIV infection.

The immunoprophylactic approach has also been found to be ineffective for some rotavirus infections. So, since 2002, infectious diseases caused by two members of the zoonotic family have become widespread among mankind (up to the outbreak of an epidemic): severe respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV). Through-

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

out the entire "therapy" course there was a shortage of antiviral drugs for the effective treatment of diseases. This situation is partly due to the lack of a clear classification of viruses that are non-pathogenic and pathogenic for humans (including coronaviruses), the absence of such a concept as "bacteriophage". To this day, a unified approach continues to dominate in modern virology, mistakenly associated with a stereotypical interpretation of concepts such as transcription, translation, replication, which appear in generalized, but not completely formed "schemes" reflecting the toxiconomic characteristics of viruses pathogenic for humans, including coronaviruses.

The drugs used to treat COVID-19, the vast majority of which are only symptomatic, are not always effective. So, during long-term treatment, possible complications often arise in individual organs and even systems, which, to a certain extent, is due to the high mortality rate of patients infected with coronavirus (SARS-CoV-2).

Due to the current situation, it seems urgent to create more effective vaccines against COVID-19, which (with varying success) are being developed in a number of developed countries: United States, United Kingdom, Sweden, France, Russia and China.

In the period from 2019 to 2020, 213 vaccines were at various stages of biotesting and commercial production, 66 of which at the stage of clinical trials, and 9 were still subjected to large-scale randomized control [*Klowden K et al., 2020; Soegiarto G, 2020*].

In all countries that are involved in creating vaccines, the principle is based on the progressive implementation of the following stages: preclinical, clinical and post-licensed according to an identical register of scientific and clinical trials. Currently, various teams involved in the implementation of programs are using various scientific and methodological approaches to create vaccines aimed at ensuring immunological activity and relative safety [*Jeyanathan M et al., 2020; Hsu Y et al., 2020; Klowden K et al., 2020; Soegiarto G, 2020*]. In our opinion, when choosing a commercial vaccine, individuals should be aware of the basic characteristics of licensed vaccines.

1. Vaccines prepared on the basis of attenuated and inactivated viruses. Live virus has been weakened through mutations of key virulence factors. Complete inactivation of the virus can be caused by various physicochemical factors: radiation, heat treatment, chemical sterilization [*Kaur S, Gupta Y, 2020; van Riel D, de Wit E, 2020*]. Despite the relatively high immunogenicity of vaccines, especially those prepared based on an attenuated live virus, one of the significant drawbacks is only partial compliance with the requirements to ensure a high level of safety for SARS in the production process [*Klowden K et al., 2020; Netea M et al., 2020*].
2. Vaccines made from purified proteins (protein-based vaccine), which are isolated from the virus, or cells that have previously been infected with the virus. For this purpose, recombinant cells which are endowed with the ability to express a virulent protein are also used.
3. Vaccines using a recombinant virus, also endowed with genes of a search antigen - a specific antigenic determinant (virus-based vaccine). A recombinant virus is able to replicate (replicative virus), or deprived of this ability (non-replicative virus).
4. Vaccines prepared due to DNA and RNA technical processing (DNA and RNA based vaccine), where DNA and RNA of the required antigen are inserted into the host cells. In the host cells, the apparatus of their genes begins to function, followed by the expression of antigens that cause a specific immune response.
5. Vaccines prepared using antigen presenting cells - APC 9 (antigen presenting cell based vaccine).
6. In addition to active immunization, that is, vaccination, a methodological approach has also been tested based on the induction of passive or adoptive immunity. Serum or plasma of patients who have recovered from COVID-19 (convalescent plasma therapy) is used. Serum and plasma contain polyclonal antibodies directed to various antigenic determinants of SARS-CoV-2.

A number of commercial vaccines based on using a recombinant virus, as well as vaccines prepared during DNA and RNA processing, which are endowed with the genes of the search antigen, are selectively aimed at blocking a specific antigen receptor on SARS-CoV-2 surface. Therefore, vaccination may lead to "undesirable" situation associated with a relatively short-term effect of the vaccine. In our opinion, this situation is due to the fact that more than one antigenic determinant is in-

volved on the surface of SARS-CoV-2. That is why such vaccines are effective only for a relatively short period of time, regardless of whether the modified (recombinant) virus has the ability to replicate or not. In both cases, the immunological activity of the vaccine is weak. In comparative terms, the immunological activity is higher when using the replicative virus.

As a result of a relatively short-term effect, it is now necessary to re-vaccinate after a certain period of time (in most cases, one month after the first vaccination).

At the same time, certain precautions should be taken into account while re-vaccinating. We are talking about the amount of specific antibodies after the first vaccination. Apparently, if the level of antibodies is high, in our opinion, the re-vaccination should be postponed, since re-vaccination with the same weakened or dead vaccines may result in a hyperimmune state with a sharp increase in antibodies to SARS-CoV-2, with all undesirable consequences that, even in practically healthy individuals, can be associated with varying degrees of innate immunological activity. In such situation, it is impossible to exclude the occurrence of multidirectional disorders in the immune status, manifested selectively in the form of "antibody-dependent enhancement" phenomenon, as in cases of using the vaccine against Dengue and SARS-CoV [*Bhopal S, Nielsen M, 2020; Su S et al., 2020*], or in the form of induction of the "active immunological tolerance" state. Both abovementioned symptom complexes of immunological disorders that arise in individuals as a result of revaccination can be accompanied by severe dystrophic and inflammatory processes, not only within the immune system, but also can extend to other integrative systems of the body.

In a widespread international "company" for testing and introducing vaccines, specialists (primarily virologists, immunologists and molecular biologists) have missed one important circumstance. We are talking about the features of the "structural organization" of SARS-CoV-2, and more specifically, about the possibility of the presence of more than one antigenic determinant on the surface of SARS-CoV-2 virus.

Currently, there is a dominating concept, according to which SARS-CoV-2 begins to infect a target cell through a single receptor mechanism, due to the interaction of receptor binding domain of S protein with angiotensin-converting enzyme-2 (ACE-2). For the most part, studies in this direction were based on the established fact, that SARS-CoV-2 S-protein has pronounced antigenic properties. This property of S-protein is used in the development of a number of vaccines, as well as against COVID-19, since the same S-protein acts as a permitting factor by which SARS-CoV-2 infects target cells of the host organism [*Chen Y et al., 2019; Copershini F et al., 2020; Mago S et al., 2020; Sugihartono T et al., 2020*].

As we mentioned above, the activation of the immunological reactivity of patients suffering from COVID-19 and a healthy contingent of individuals who have undergone vaccination, aimed at developing specific antibodies against SARS-CoV-2, is carried out by blocking the antigenic activity of the coronavirus S-protein. Of course, binding antibodies to S protein should lead to conformational changes of the protein molecule. As a result, the previously "hidden" amino acid binding sites are expressed and structures with antigenic potencies appear.

It is also possible that such processes arise in a particularly prevalent situation when, as a result of vaccination, only specific (individual) antigenic determinants of the S-protein are blocked and new microstructures of this protein are "opened", which also have antigenic potencies. This situation, to a certain extent, elucidates the possible appearance of new SARS-CoV-2 "strains".

Undoubtedly, if our hypothesis turns out to be consistent, there will be a need to create new vaccines aimed at synthesizing antibodies to new, previously hidden antigenic determinants of the SARS-CoV-2 S-protein. On the other hand, it is possible that latent antigenic determinants are localized on the surface of SARS-CoV-2 virus, in areas different from the localization of the S-protein.

It should be noted that SARS-CoV and SARS-CoV-2 share a certain structural identity. So, the genomic and amino acid sequence in both coronaviruses is almost identical [*Angeletti S et al., 2020; Lu R et al., 2020; Sugihartono T et al., 2020; Xu Z et al., 2020*]. In our opinion, it is also important that SARS-CoV enters target cells by binding to ACE-2 as a receptor [*Du L et al., 2009*]. That is why, it can be hypothesized that a similar receptor

mechanism can be activated when SARS-CoV-2 appears as a human pathogenic coronavirus [*Hoffman M et al., 2020*].

At the same time, specialists, who are in search for possible antigenic determinants located on the surface of SARS-CoV-2, should pay attention to issues related to the biological activity of angiotensin-converting enzyme-2 in mammals. Thus, ACE-2 is functioning via the receptor mechanism in the cells of many organs and tissues. Of course, this is an evolutionarily formed mechanism for the balanced interaction of angiotensin-2 with ACE-2, aimed at regulating blood pressure at the levels of all integrative systems of the body.

It's not excluded that cardiovascular complications during COVID-19 also arise as a result of the competition between SARS-CoV-2 and angiotensin-2 for ACE-2 receptors, which are functioning in blood vessels (coronary, peripheral, microcirculation systems).

That is why vaccines prepared based on S-protein antigen cannot serve as the only "panacea" for immunoprophylaxis in COVID-19. So, even if taking into account the fact that ACE-2 in COVID-19 may have a cross-interacting potential in relation to both angiotensin-2 and SARS-CoV-2, this functioning mechanism, in our opinion, should not be considered the only one, especially defining.

In this regard, it is enough to cite very informative data about another (besides ACE-2) receptor mechanism related to interaction with CD-147 [*Leonardi A et al., 2020; Shilts J et al., 2021*]. Thus, the CD-147 receptor was identified while studying porcine reproductive and respiratory syndrome virus (PRRSV), when viral invasion into cells was markedly activated by the interaction of CD-147 with the viral spike protein [*Duan L et al., 2020*].

Moreover, the use of antibodies against CD-147 turned out to be very effective, since it prevented the penetration of viruses into target cells by blocking CD-147 [*Lebeau G et al., 2020; Wang K et al., 2020*]. Based on conducted studies, according to the authors, CD-147 is also functioning in COVID-19.

According to our point of view, CD-147 (Bazigin), located on the erythrocyte membrane, binds to SARS-CoV-2 via the receptor mechanism, thereby ensuring the penetration of coronavirus into these cells [*Zilfyan A et al., 2020; Avagyan S et al., 2021b*]. In the same publications, we made the assumption that long-term persistence of SARS-CoV-2 occurs not only under conditions of consumption of polyamines localized in parenchymal organs, but also as a result of the coronavirus penetration into erythrocytes, which at least act as a reserve and transport of polyamines. Upon penetration into erythrocytes, SARS-CoV-2 begins to "absorb" polyamines localized in them. The process is accompanied by pronounced dystrophic changes in the circulating blood erythrocytes, as well as in the internal organs localized in the microhemocirculation system, which ultimately ends with blood clot formation. Of course, this is only one possible mechanism from the general cascade of reactions leading to the blood clot formation in COVID-19, with all the ensuing consequences and, first of all, the occurrence of ischemic lesions of internal organs and thromboembolism.

As we have noted earlier, the main doubts and concerns of a wide contingent of healthy individuals, regardless of their region of residence, level of intelligence, socio-economic status and national characteristics, arise in connection with the need for their mandatory vaccination against COVID-19.

In general, topical situational issues that are put forward by the population of many countries can be expressed in the following points.

First point: Is it worth getting vaccinated at all if complications may arise that lead to death even in practically healthy individuals, not to mention the elderly with chronic diseases?

Second point: In case of making positive decision (that is, the desire to be vaccinated), the question naturally arises in terms of choosing a vaccine, since vaccines are used in different countries, in the production of which multi-vector scientific, methodological and technological approaches are used, which are presented in an annotated version in the article.

Third point: Is there a need of re-vaccination within a short period after the first vaccination? As a rule, it is recommended to re-vaccinate in 14-30 days after the first vaccination. In this regard, there are concerns about the low efficacy (weak selective immunogenic activity) of vaccines.

Fourth point: How expedient, if not contraindicated, is to "fully" vaccinate patients in the recovery period, as well as over the next one to two months, if they have high levels of SARS-CoV-2 antibodies?

Fifth point: In case of re-vaccination, it is nec-

essary to find out whether it is possible to carry out the second vaccination with the use of a commercial vaccine of another manufacturer, especially since many developing countries do not currently have such a vaccine that has been introduced during the first vaccination.

Sixth point: How competent is it to vaccinate a wide range of healthy individuals against COVID-19 and influenza - at the same time or with the shortest time interval?

Unfortunately, in our opinion, these are not all the issues that specialists studying aspects related to the occurrence, course, prognosis and prevention of COVID-19 should pay attention.

At the same time, we will try to answer the questions raised by us, without pretending to be an exhaustive interpretation of some of them.

Regarding the first point concerning mass vaccination. Carrying out mass vaccination is certainly necessary, since, unfortunately, we currently do not have effective means of pathogenetic and symptomatic therapy for COVID-19.

Vaccination today is the only "radical" approach to combating the coronavirus pandemic, covering a wide contingent of healthy individuals of different ages, as well as people with certain chronic diseases.

The second point, concerning the choice of vaccines produced in different countries, it will not always be possible for the population to choose the desired vaccine (that is, similar to the first vaccine), because it depends on which vaccine this or that country currently has.

In this regard, the authorities responsible for organizing measures to combat COVID-19 (administrative and executive, health care, with the involvement of "competent" media) should conduct a wide outreach and educational work, focusing on the biotechnological characteristics of various produced vaccines, and, first of all, those vaccines that the country currently has. The general public should be informed about the relative effectiveness of the used vaccines, and, moreover, their harmlessness - in terms of the risk of complications.

Regarding the third point, concerning the need for revaccination (second). In our opinion, firms and institutions - manufacturers of vaccines in many countries, hastened to preclinical and clinical testing of vaccines and obtain a license for their production. So, the majority of vaccines, despite the relative "harmlessness", turned out to be weakly immunogenic. Moreover, various scientific institutions - developers and commercial firms have applied various biotechnological approaches based on the existing "schemes" for the creation of vaccines, which, as we have indicated above, are far from perfect for objective reasons. Naturally, the process of producing specific antibodies in each specific case is not able to block all detected antigenic receptor determinants that are on the surface of SARS-CoV-2. In our opinion it is because more pathogenic strains of SARS-CoV-2 appear, since the coronavirus must adapt to new conditions in order to ensure its further persistence in the macroorganism.

Concerning the fourth point, the vaccination of patients during recovery period. In our opinion, there is no need to vaccinate recovered patients during this period (we are talking about re-vaccination with the same commercial vaccine that was used for the first time), since the initial cellular and subsequently humoral immune responses are selectively directed to the production of specific antibodies, unfortunately, only to the specific antigenic determinant of SARS-CoV-2.

That is why, it is necessary to conduct a separate company, including mass agitation of the population, in order to determine the level of antibodies to coronavirus (SARS-CoV-2). In case of a high level of antibodies in reconvalescents, the latter do not need vaccination in the early recovery period. Apparently, in this current situation, a diagnostic analysis for the determination of antibodies to SARS-CoV-2 should be carried out a second time, that is, 1-2 months after recovery. However, if antibodies to coronavirus are not detected in the early recovery period, or are determined in extremely low quantities, such patients must be vaccinated.

As to the fifth point, the question of secondary vaccination, with the use of another commercial vaccine (not the one that was used at the first vaccination), it is necessary to adhere to the following tactics. So, before the second vaccination, it is necessary to determine the level of antibodies in the macroorganism after the first vaccination. Even in cases where antibodies after the first vaccination are determined in optimal, and even in relatively high quantities, it is possible to vaccinate with an-

other commercial vaccine. However, a prerequisite for secondary vaccination should be the only justified scientific and methodological approach based on the production of antibodies to other antigenic determinants of SARS-CoV-2, that is, different in conditions of the first vaccine application.

The sixth point, the issue of simultaneous vaccination (with an interval of several days) against SARS-CoV-2 and the influenza virus, n our opinion, currently there is not and cannot be an intelligible answer to this question.

Therefore, we can only discuss a number of theoretically justified proposals, testifying against the joint vaccination against the influenza virus and SARS-CoV-2.

So, with the possible development of a "scenario" when the structural antigenic determinants of the influenza virus and SARS-CoV-2 are far from identical, after prophylactic vaccination against the influenza virus and SARS-CoV-2, a very undesirable situation may arise when the immune system of the macroorganism begins to work on "two fronts" - in terms of simultaneous production of both antibodies to the influenza virus and to SARS-CoV-2.

Therefore, it is possible that in the process of vaccination with both vaccines, a state of immune overvoltage may occur, which is often referred to as "hyperreactivity of the immune system". It should be noted that a similar state of hyperactivity of the immune system is described even in the course of a monoviral infection caused by SARS-CoV-2, when violations of the "systemic inflammatory response" (systemic inflammatory response) is largely due to the occurrence of a "cytokine storm" [*Chen Y et al., 2019; Coperchini F et al., 2020; Maggo S et al., 2020*].

It is also possible that functional overstrain in the system of immunogenesis organs, ultimately, can lead to the development of "active immunological tolerance". This current situation allows both the cancellation of the reactions responsible for the production of specific antibodies against both SARS-CoV-2 and the influenza virus. A similar situation, in particular, can also lead to the emergence of the so-called "cytokine storm", in the development of which pro-inflammatory cytokines of the already directed immunosuppressive spectrum of action begin to dominate among immunity mediators.

Unfortunately, the concept of "cytokine storm" is often manipulated by many researchers who try to interpret regional and general immunopathological disorders arising in COVID-19 only in terms of directed activation and/or inhibition of "immunity mediators", and in a narrower sense – cytokines. It has long been known that the concept of "cytokine storm" appeared in the study of the immunopathogenesis of a number of severe diseases, with a "systemic inflammatory response" characteristic of all of them. At the same time, for the most part, the cytokine response was characterized by stereotypical shifts in the process of production, distribution and implementation of "immunity mediators", both pro-inflammatory and anti-inflammatory spectrum of action. In this regard, the changes found in the immune system, in particular those associated with the synthesis and effects on target cells of both pro-inflammatory and anti-inflammatory cytokines, cannot be considered only pathognomonic for COVID-19 course. That is why we recommend the researchers of various specialties involved in the development of aspects on COVID-19 immunopathogenesis, to use the concept of "cytokine storm" with a certain amount of caution and responsibility.

In conclusion, we believe that the vaccination process is currently the only "international immunoprophylaxis company" that will prevent the occurrence of COVID-19 in most cases.

There is no doubt that new "hidden" antigen-binding sites on the surface of SARS-CoV-2 will be discovered in the near future, which will serve as a basis for finding new modern technologies in the process of creating new, more effective vaccines.

REFERENCES

1. *Angeletti S, Lo Presti A, Cella E, Ciccozzi M (2016).* Molecular epidemiology and phylogeny of Nipah virus infection: A mini review. Asian Pacific Journal of Tropical Medicine. 9(7): 630-634
2. *Avagyan SA, Muradyan AA, Zilfyan AV (2021a).* Certain approaches while choosing the strategy of COVID-19 pathogenetic therapy and immunoprophylaxis. The New Armenian Medical Journal. 15(2): 4-18

3. *Avagyan SA, Zilfyan AV, Muradyan AA (2021b).* The need to add a "polyamine-deficient" diet in the food registry of COVID-19 patients. The New Armenian Medical Journal. 15(2): 19-34
4. *Avagyan SA, Zilfyan AV, Muradyan AA, Ghazaryan VJ, Ghazaryan HV (2020).* New perspectives for the treatment and prevention of COVID-19 infection. The role of polyamine-dependent mechanisms in the life cycle of RNA and DNA viruses in mammals. The New Armenian Medical Journal. 14(4): 108-122
5. *Bhopal S, Nielsen M (2021).* Vaccine hesitancy in low- and middle-income countries: Potential implications for the COVID-19 response. Arch Dis Child. 106: 113-114
6. *Chen T, Wu D, Chen H, Yan W, Yang D., et al (2020).* Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 368: m1295
7. *Chen Y, Diao B, Wang C, Chen X, Liu Y., et al (2020b).* Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19). Front Immunol. 11: 827p
8. *Chilingaryan TG, Poghosyan HV, Sargsyan KM, Hovhannisyan HB, Karapetyan K.H., et al (2021).* The role of anticoagulation in preventing myocardial infarctionand improving the outcomes among COVID-19. The New Armenian Medical Journal. 15(2); 35-41
9. *Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M (2020).* The Cytokine storm in COVID-19: Anoverview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev. 53: 25-32
10. *Devaux CA, Rolain J-M, Philippe Colson P (2020).* Didier Raoult, New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?, International Journal of Antimicrobial Agents. doi:https://doi.org/10.1016/j.ijantimicag.2020.105938
11. *Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S (2009).* The spike protein of SARS-CoV - A target for vaccine and therapeutic development. Nat Rev Microbiol. 7(3): 226-236
12. *Duan L, Zheng Q, Zhang H, Niu Y, Lou Y, Wang H (2020).* The SARS-CoV-2 Spike Glycoprotein Biosynthesis, Structure, Function, and Antigenicity: Implications for the Design of Spike-Based Vaccine Immunogens. Front Immunol. 11: 576622
13. *Ferrari D, Motta A, Strollo M, Banfi G, Locatelli M (2020).* Routine blood tests as a potential diagnostic tool for COVID-19. Clinical Chemistry and Laboratory Medicine (CCLM). 58(7): 1095-1099
14. *Guo T, Fan Y, Chen M, Wu X, Zhang L., et al (2020).* Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiology. 5(7): 811-818
15. *Hoffman M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T., et al (2020).* SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. 181(2): 271-280.e8
16. *Hsu YC, Wu HC, Hsu YF, Chen PY, Chiang JR. Covid19: Global Progress in Developing Vaccines and Mechanisms for Equitable Distribution. Epidemiol. Bull. 2020; 36(16): 95*
17. *Huang C, Wang Y, Li X, Ren L, Zhao J., et al (2020).* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 395(10223): 497-506
18. *Jeyanathan M, Afkhami S, Smaill F, Miller MS, Lichty BD., et al (2020).* Immunological considerations for COVID-19 vaccine strategies. Nat Rev Immunol. 20(10): 615-632
19. *Kaur SP, Gupta V (2020).* COVID-19 Vaccine: A comprehensive status report. Virus Research. 288: 198-114
20. *Klowden K, Jackson J, Lin MC, Hanigan S (2020).* Examining Arizona's Technology and Research Initiative Fund (TRIF). Milken Institute. 31p
21. *Lebeau G, Vagner D, Frumence É, Ah-Pine F, Guillot X., et al (2020).* Deciphering SARS-CoV-2 Virologic and Immunologic Features. International Journal of Molecular Sciences. 21(16): 5932
22. *Leonardi A, Umberto, Paola B (2020).* Ocular Surface Expression of SARS-CoV-2 Receptors. Ocular Immunology and Inflammation. 28(5): 1-4

23. *Lu R, Zhao X, Li J, Niu P, Yang B., et al (2020).* Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The Lancet. S0140673620302518
24. *Maggo S, Dhull P, Dubey AP, Brashier D, Karan A., et al (2020).* Cytokine Storm Syndrome in COVID-19: Diagnosis and Management Strategies. 10(5): 140-149
25. *Melik-Nubaryan DG, Sakanyan GG, Tadevosyan AE, Zeynalyan NA (2021).* Strengthening the role of the primary health care in the covid-19 response: evidence from Yerevan. The New Armenian Medical Journal. 15(2): 69-81
26. *Netea MG, DomÃnguez-AndrÃ©s J, Barreiro LB, Chavakis T, Divangahi M., et al (2020).* Defining trained immunity and its role in health and disease. Nat Rev Immunol. 20: 375-388
27. *Pandey SC, Pande VS, Upreti S, Samant M (2020).* Vaccination strategies to combat novel corona virus SARS-CoV-2. Life Sciences. 256: 117956
28. *Poland GA, Ovsyannikova IG, Kennedy RB (2020).* SARSCoV-2 immunity: review and applications to phase3 vaccine candidates. Lancet (London, England). 396(10262): 1595-1606
29. *Shi S, Qin M, Shen B, Cai Y, Liu T., et al (2020).* Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 5(7): 802-810
30. *Shilts J, Crozier TW, Greenwood EJ, Lehner PJ, Wright GJ (2021).* No evidence for basigin/CD147 as a direct SARS-CoV-2 spike binding receptor. Scientific Reports. 11(1):
31. *Sisakian HS, Harutyunyan GH, Hovakimyan MH, Hovhannisyan MR, Aghayan SA (2021).* Pacemaker Lead-Associated Pulmonary Embolism in Patient with COVID-19 Infection. The New Armenian Medical Journal. 15(2): 42-45
32. *Soegiarto G (2020).* Vaccination For Coronavirus Disease 2019: Opportunity, Hope And Challenges, The New Armenian Medical Journal. 14(4): 58-66
33. *Su S, Du L, Jiang S (2021).* Learning from the past: development of safe and effective COVID-19 vaccines. Nat Rev Microbiol. 19: 211-219
34. *Sugihartono T, Arafah N, Yamaoka Y, Miftahussurur M (2020).* Gastrointestinal Manifestations in COVID-19 Infection. The New Armenian Medical Journal. 14(4): 70-81
35. *Supit VD, Helena MG, Alfares MA, Angky VS, Saputra A (2021).* Hematologic Parameters as Potential Diagnostic Tools for Covid-19 In Emergency Setting. The New Armenian Medical Journal. 15(2): 46-55
36. *Tang, N, Li D, Wang X, Sun Z (2020).* Abnormal Coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis. 18(I4): 844-847
37. *van Riel D, de Wit E (2021).* Next-generation vaccine platforms for COVID-19. Nat Mater. 19: 810-812
38. *Wang K, Huang W, Chen R, Lin P, Zhang T., et al (2021).* Di-methylation of CD147-K234 Promotes the Progression of NSCLC by Enhancing Lactate Export. Cell Metabolism. 33(1): 160-173.e6
39. *Xu Z, Shi L, Wang Y, Zhang J, Huang L., et al (2020).* Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 8(4): 420-422
40. *Zhou F, Yu T, Du R, Fan G, Liu Y., et al (2020).* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 395(10229): 1054-1062
41. *Zilfyan AV, Avagyan SA, Muradyan AA, Ghazaryan VJ, Ghazaryan HV (2020).* Possible role of aliphatic polyamines in the inhibition process of daughter viruses replication in COVID-19 infection. Expediency of adding -difluoromethylornithine to the registry of drugs for COVID-19 infection. The New Armenian Medical Journal. 14(4): 4-15
42. *Zilfyan AV, Muradyan AA, Avagyan SA (2021).* Possible polyamine-dependent mechanisms indicating the systemic characteristics of COVID-19. New approaches in the correction of symptomatic therapy of COVID-19. The New Armenian Medical Journal. 15(3): 4-15

THE NEW ARMENIAN MEDICAL JOURNAL
Vol.16 (2022). No 1

CONTENTS

THE NEW ARMENIAN MEDICAL JOURNAL

Vol.16 (2022). No 1

The Journal is founded by
Yerevan State Medical
University after M. Heratsi.

Rector of YSMU

Armen A. Muradyan

Address for correspondence:

Yerevan State Medical University
2 Koryun Street, Yerevan 0025,
Republic of Armenia

Phones:

(+37410) 582532 YSMU
(+37410) 580840 Editor-in-Chief

Fax: (+37410) 582532

E-mail: namj.ysmu@gmail.com, ysmiu@mail.ru

URL: http//www.ysmu.am

Our journal is registered in the databases of Scopus, EBSCO and Thomson Reuters (in the registration process)

SCOPUS

EBSCO

THOMSON REUTERS

Copy editor: Tatevik R. Movsisyan

Printed in "VARM" LLC
Director: Ruzanna Arakelyan
Armenia, 0018, Yerevan,
Tigran Mec 48, 43
Phone: (+374 91) 19 29 00,
E-mail: armana6@mail.ru