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Authors: Aziz Rodan Sarohan[1]

Affiliations: Department of Obstetrics and Gynecology, Medicina Plus Medical Center, Istanbul Turkey[1]

Orcid ids: 0000-0002-5794-688X[1]

Contact e-mail: azizrodan@gmail.com

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Lessons from a self-terminating pandemic: Vaccination, vitamin A deficiency and a brief epidemiological overview

Aziz Rodan Sarohan

Department of Obstetrics and Gynecology, Medicina Plus Medical Center, İstanbul, Turkey

Email; azizrodan@gmail.com

Summary

Declared a pandemic by WHO in March 2020, COVID-19 infected more than 460 million people, causing the death of more than six million people. With the Omicron variant becoming the dominant form, COVID-19 ended on its own, leaving behind serious socioeconomic traumas and dozens of chronic inflammatory diseases. With the transformation of COVID-19 into seasonal flu, it is predicted that it will no longer cause serious socioeconomic and health problems on a societal scale. During the pandemic process, it was tried to stop the epidemic with extraordinary measures such as hygiene, quarantine, closure of schools, travel restrictions, filiation practices, financial and psychosocial support, and effective use of mass media. These measures undoubtedly slowed the pace of the epidemic somewhat. It was anticipated that vaccines would not provide long-term protection against COVID-19 due to mutations that develop so frequently in SARS-CoV-2. Despite this, researchers focused heavily on vaccine development throughout the process. With the vaccines developed in this process, at least one dose of the COVID-19 vaccine was given to approximately 4.9 billion people as of April 2021. The dictation of vaccines as the only and most effective solution in the fight against the pandemic prevented the detection of micronutrient deficiencies such as vitamin A deficiency, which facilitated the epidemic, on a societal scale and other alternative solutions. Some studies show that vitamin A deficiency may have played a role in the transmission of COVID-19 and the development of the severe clinical picture. The pandemic is coming to an end before the main reason or reasons underlying the fact that COVID-19, the biggest epidemic of our age, mostly affects western societies and is fatal in the elderly population living in big cities, are not clarified. In order to find the answer to this intriguing question, community-based dietary habits and epidemiological scans for micronutrient deficiency such as Vitamin A deficiency were not conducted. At a time when people began to lose their confidence in COVID-19 vaccines, SARS-CoV-2 underwent a heavy mutation, as the evolutionary process required, and COVID-19 turned into a flu-like infection.

Keywords: COVID-19, vitamin A, vitamin D, WHO, CDC, FDA, pandemic, big pharma, vaccines, drugs, epidemiology, medical ethics, medicolegal, public health, relations of interest
Introduction

In this review, some determinations about vaccine and drug development studies, the policies of WHO, CDC, NIH, FDA, and EMA, which are regulatory centers in this field, and the effect of the big pharma on the shaping of these policies, as well as the relationship between vitamin A and COVID-19 and its use in previous epidemics. Some facts are brought to the fore. The ball of interest-based relations shaped during the pandemic process has prevented this most important epidemic of our age from being approached objectively and producing effective and correct solutions. Therefore, epidemiological studies have been neglected to determine nutritional and demographic, and environmental factors such as micronutrient deficiencies that facilitate the epidemic. This policy, which is maintained during the pandemic process, needs to be examined and questioned in order to effectively fight epidemics that may arise in the coming years and to design institutions accordingly.

What kind of a mission did WHO, CDC, NIH, FDA, and EMA undertake in vaccine and drug studies that were primarily supported during the pandemic process and which were not very successful, and where was big pharma in this equation (1)? Carrying out vaccine development studies through only a few companies has led to a monopoly in this field (2). These companies hid behind patent protection laws and prevented the free production of vaccines for COVID-19 (3). Thereupon, WHO stated that mRNA vaccine technology will be transferred from the vaccine center in South Africa to five countries (Bangladesh, Indonesia, Pakistan, Serbia, and Vietnam) in order to overcome the patent barrier and it will approve the infrastructure studies for the production of mRNA vaccines in these countries (4).

The drawbacks of the solution, which were found in the form of tendering the pandemic process to the private sector, were beginning to emerge. This remedy also became an obstacle to finding real solutions that could be quick and effective to end the pandemic. In this respect, it is very important to examine these relations and to clarify and discuss the secrets behind the scenes in order to draw some lessons for the future and to construct the future well. Knowing what happened in this process is a fundamental human right based on the right to information law, which is evaluated and accepted in international human rights law (5). For this purpose, the whole process, including the political and bureaucratic manipulations used to manage this process, from the preventive measures taken during the pandemic process to the vaccine and drug development studies, should be questioned and discussed in detail.

COVID-19 pandemic, outbreak management, vaccines, and drug studies

Despite the high technological and scientific developments in our age, effective drugs and vaccines against COVID-19 could not be developed during the pandemic process (6). Due to the measures and social restrictions taken to prevent the epidemic, people had to be confined to their homes for two years. The COVID-19 pandemic has killed more than six million people and caused severe socioeconomic devastation (7). However, mankind, who had made the industrial revolution, realized its technological development and turned into information and scientific societies, had to be able to easily overcome this epidemic.
World societies, especially developed western societies, were now using artificial intelligence in daily life and scientific studies (8). This new technology detected diseases when and where they first appeared, was enabling rapid action to be taken to prevent the spread of epidemics (9). But unfortunately, despite the past two years and all efforts, neither the treatment of COVID-19 nor its source of origin could be determined clearly.

At a time when people began to lose their trust against vaccines dictated as the only solution in the fight against the pandemic, SARS-CoV-2 underwent a heavy mutation, as the evolutionary process required, and turned into a flu-like infection (10). Despite all the vaccine and drug studies and mixed relationships, the pandemic was finally ending on its own. During the pandemic process, we woke up every day with the news of a new mutation and a new variant. New mutations and emerging new variants of SARS-CoV-2 were always kept their place in the top list of news headlines of international media organizations (11). Until the Omicron variant appeared. Initially, it was reported that Omicron was more contagious than other variants and spread faster. Although this situation created an atmosphere of panic at first, it was soon understood that Omicron caused a milder disease picture compared to the previous variants, and people were relieved (10,11). With the transformation of COVID-19 into a simple flu infection with Omicron, researchers finally began to believe that the pandemic would end (12).

What lesson should we learn from this pandemic in order to build the future correctly? What kind of a mission did WHO, CDC, NIH, FDA, and EMA undertake in the vaccine and drug studies carried out during the pandemic process, which were not very successful (13,14,15)? Where was Big pharma in this equation (14,15)? Although it is not possible to find the answers to all these questions immediately, we have to wait for the storm to pass and the dust and smoke to clear to see the whole picture. Only then can we have the chance to see the revolving cabinets with all their nakedness during the pandemic process. However, groups that keep their own interests above public health and turn this devastating pandemic process into an economic rent will not stay idle after the pandemic to prevent their dirty underwear from being exposed.

Even at the beginning of the pandemic process, COVID-19 turned into a serious economic rent, and the lives and future of millions of people were unfortunately left in the hands of commercial institutions and some interest groups (1). Some countries, which turned the COVID-19 pandemic into an economic rent, found themselves in the biggest economic and social crisis in history due to the serious socioeconomic traumas brought by the pandemic (16). COVID-19 triggered the most serious economic crisis after the great economic depression after World War II, which is a human tragedy (17,18). In this process, some politicians, some administrators, and bureaucrats in regulatory centers such as WHO, CDC, and FDA acted in a clear relationship of interest with Big Farma and some research centers. The cooperative relationship between these organizations was questionable (19,20). The influence of pharmaceutical companies on regulatory centers has been the subject of much debate, even in the US House of Representatives, and has been officially recorded (19). It is obvious that this tangle of dubious relations in the pandemic process needs to be clarified without wasting is time.
Thanks to the prominence of the idea that the most effective method in the fight against the COVID-19 pandemic is to develop vaccines and to vaccinate the community, and the development of the technological infrastructure, many vaccines have been developed against COVID-19 at an unprecedented and unprecedented rate in history (21). Among these, there were also new technology mRNA vaccines, which were produced for the first time in this pandemic and had a chance to be applied. These vaccines, which were prepared by spending large funds, started to be used after the approval of regulatory centers very quickly due to the emergency caused by the pandemic (22). Very serious and fatal side effects such as thrombosis and brain infarction were observed in some of these vaccines, which were produced and started to be used very quickly by accelerating the phase studies (23,24). Thereupon, some vaccines were withdrawn from the market (25). There were always doubts in the society and scientific circles that these vaccines, whose long-term effectiveness against the virus was not clearly known, would be successful in the fight against the epidemic.

We did not have a clear idea about the long-term results of the vaccines that were started to be used with emergency use permission before the licensing process was completed (26). It was unclear whether these vaccines would be effective against SARS-CoV-2 in the long term due to emerging new SARS-CoV-2 variants. There has never been a common consensus in the scientific community on this issue either. There has also always been doubts about the side effects of vaccines. Another problem with vaccines was production capacity and logistical support problems (27). Likewise, a widespread and effective production standard for vaccines could not be achieved due to license and patent problems. Again, due to logistical and economic reasons, vaccines could not be distributed to countries fairly. Despite all the calls of the World Health Organization, people in 3rd World countries remained unvaccinated. Unfortunately, all these problems continued during the pandemic process.

**How effective have vaccines been against the mutagenic SARS-CoV-2?**

It was soon understood that SARS-CoV-2 mutated very frequently and could escape the immunity provided by vaccines. In this regard, mRNA vaccines produced with a new technology rather than conventional vaccines were relied upon in the fight against the pandemic (28). However, it was soon seen that mRNA vaccines did not provide full protection against emerging new SARS-CoV-2 variants. Even if these vaccines provide temporary protection against COVID-19, it has been expressed from time to time by the manufacturers that these effects may be possible for a maximum of 6 months. Pfizer-BioNTech and Moderna, the manufacturers of mRNA vaccines, declared that two doses of vaccination may not be sufficient due to emerging new SARS-CoV-2 mutants, and a third dose and even a fourth dose of vaccine may be needed with an interval of six months (29). In fact, these companies have declared that due to new SARS-CoV-2 variants, it may be necessary to be revaccinated with updated vaccines every year against COVID-19, as is the case with influenza vaccines. It was also stated that this practice could become permanent. Another option suggested by the companies was the recommendation of repeating the vaccine doses with vaccines with different contents.
Every method that comes to mind in the fight against the epidemic and vaccine applications was tried to cope with the pandemic. This approach exhibited in vaccine applications was not rational and could not remove doubts about the efficacy and safety of vaccines (30). There were also safety concerns about the long-term side effects of vaccines. An unforeseen and long-term potential danger of such vaccine applications is the triggering of autoimmune and inflammatory diseases and latent infections (31). It is known that continuous administration of antigens to the body with repeated vaccinations causes a continuous stimulation in the immune system and triggers chronic inflammatory and autoimmune diseases (31).

It has been reported in the literature that nasal carriage of SARS-CoV-2 is increased in persons fully vaccinated with mRNA vaccines, and the carrier rate in vaccinated individuals is higher than in unvaccinated individuals. Despite being fully vaccinated, shingles, herpes, and even HIV have been found to reactivate and cause reinfections in some individuals. Due to commercial concerns, the fight against the epidemic was carried out only through vaccines. Therefore, while vaccine studies came to the fore, drug studies were pushed into the background and drug studies that could be effective against SARS-CoV-2 were interrupted. The emergence of new SARS-CoV-2 mutants was reducing the effectiveness of vaccines in the fight against the pandemic day by day. Despite being vaccinated, the number of people who have had severe COVID-19 and have died is not small.

During the pandemic process, we woke up every day with the news of a new mutation and a new variant. New mutations of SARS-CoV-2 and emerging new variants have always kept their place in the top list of news headlines of international media organizations. The change of even a single amino acid in the spike protein by mutation changes the conformational structure of the spike protein, causing the virus to escape from the immune system, making the process of developing a vaccine against the virus difficult (32). Due to the very common mutations in SARS-CoV-2, vaccines developed and produced very quickly were not effective enough against new SARS-CoV-2 variants and were constantly losing confidence. As a result, some of these vaccines, which were not effective against new variants and were prepared by spending serious funds, started to find themselves in medical waste dumps (33).

With the COVID-19 pandemic, new technology vaccines such as mRNA and vector vaccines began to enter our lives. With these vaccines, gene transfer was made to millions of people for the first time in the evolutionary process (34,35). It was soon realized that these new vaccines did not provide long-term immunity against COVID-19. However, in order to maintain the economic rent policy based on vaccines in the pandemic, a new argument has been developed that mRNA vaccines show efficacy with cellular immunity against COVID-19. This argument was based on the cellular component of the immune system in vaccine responses and was confusing. Besides we did not have definitive data about the role of T and B cells in COVID-19 immunity (39). And the SARS-CoV-2 virus, like the HIV virus, would target T cells, causing lymphopenia and a weakened immune system.

Studies have shown that the levels of antibodies produced by different vaccines in vaccinated individuals decrease over time, and the immunity provided by Pfizer and Johnson & Johnson vaccines typically lasts around six months, although it varies from person to person (38).
Immunologist Alessandro Sette of the La Jolla Institute of Immunology in California says that developing a vaccine against the coronavirus requires a large focus on antibodies, and for good reason. The antibodies are key to 'immune sterilizing', which binds to particularly important viral proteins, not only reducing the severity of the disease but also preventing infection altogether, he says. Sette says this form of protection is considered the gold standard in vaccines, but typically requires developing large numbers of antibodies (39).

These vaccines, which were prepared by accelerating the phase studies, continued to be applied to millions of people with emergency use permits, thanks to the sincere relations in the regulator centers, without fully meeting the licensing procedures. As methodologists say, the processes and results of implementing innovative solutions may not always be as simple and linear as planners envision (60). These innovative solutions often lead to some undesirable results (60,61). There is no reason why this methodological rule should not apply to mRNA vaccines as well. Likewise, the concern that mRNA vaccines might trigger some undesirable adverse health problems that go beyond their intended targets has always been a topic of discussion among a wide range of society, including researchers, politicians, and journalists (34,60). The mRNA vaccine application, which has deep doubts about its long-term results, will be discussed and discussed a lot in the coming years (34).

When it was understood that vaccines did not provide long-term protection against COVID-19, another argument developed by vaccine manufacturers and some affiliated researchers was that mRNA vaccine prevented severe COVID-19 that could lead to hospitalizations and death. Based on this argument, mRNA vaccination campaigns were continued for a while (36). Preventing serious disease is an intended goal in prophylactic drug administration. Such a thing is not the ultimate goal and goal of vaccines. The main purpose and target in pandemics and vaccination are to create sufficient and effective antibody titers to provide long-term protection with vaccination. Another important goal is to develop effective memory cells that will stimulate the immune system very quickly in case of infection with the same virus (37). Whereas, mRNA vaccines could only protect individuals until the next new variant, which corresponds to a time frame of approximately 3-5 months. Moreover, these vaccines did not prevent the carrier and spread of the virus.

Finally, until the end of February 2022, approximately 63.9% of the world population, 4.9 billion people, had at least one dose of the COVID-19 vaccine. Essentially, there was no difference between being vaccinated or having had a previous COVID-19 infection, and neither could protect against COVID-19 (38). In other words, the vaccines did not have a long-term effect on the control of the epidemic, and perhaps even had a negative effect on the spread of the epidemic, as they increased carriage. Ultimately, the antibodies developed against these vaccines were also reset, at best, after about six months.

What about the side effects of vaccines? Will the side effects of vaccines end after the pandemic?

Vaccines were presented as the only and most effective solution in the fight against the pandemic, without knowing their long-term efficacy and side effects. The policies pursued this purpose was carried out decisively under the umbrella of regulatory institutions.
Unfortunately, the NIH, CDC, and FDA, which are important decision-making centers on vaccines and drugs, also supported this policy by giving emergency use permission to these vaccines, which did not fully comply with the necessary clinical phase studies and registration procedures. These vaccines were quickly put on the production line with question marks about their efficacy and long-term protection and side effects, and continued to be administered to millions of people, with the approval of regulatory centers at the same speed (337,38,39). The strange thing is that although the speed and severity of the epidemic have decreased with Omicron, this vaccine policy is persistently tried to be continued.

While deciding to launch vaccines as the most effective weapon in the fight against the COVID-19 pandemic, it was not taken into account whether the vaccines could be effective against SARS-CoV-2, which mutates so frequently. As it can be understood from the developments experienced, the vaccines were applied to the field before this examination was fully carried out. The fact that documents and information about vaccine phase studies are not shared with the public justifies this suspicion. Questions on this subject will certainly find answers over time. However, in order to effectively combat similar epidemics that we may encounter in the future, these questions must be answered promptly and reasonable doubts must be cleared. Here, there are dubious practices that concern the health and future of all world societies on a global scale. Especially, the possibility of developing cancer and chronic inflammatory, degenerative neurological, and autoimmune diseases that may arise with the integration of mRNA vaccines, which are a kind of gene transfer, into the human genome, which is used for the first time in this pandemic process, is followed with concern in the scientific circles (34). In fact, the potential of genetic material given to the body by mRNA vaccines to be integrated into the genome of reproductive cells and to be transferred to future generations, and to cause disease in future generations is a staggering claim (34). Despite these reasonable doubts, negotiations are continuing for these vaccines to be given to children as well.

Studies that justified the suspicions about the serious side effects of mRNA vaccines soon began to appear in the literature. One of the arguments used by mRNA vaccine manufacturers against these claims was that the genetic code given by the vaccine is not integrated into the human genome. However, researchers soon demonstrated that the enzyme Polymerase Theta found in human cells can convert cytoplasmic mRNA patterns into DNA patterns and integrate them into the genome. In this way, the fact that the mRNA code delivered with vaccines could be integrated into human DNA, which is of great concern, came to light. In fact, it has been shown that the mRNA sequence given by the vaccine can be integrated into the genomic DNA of liver Huh7 cells after approximately six hours (40). Another argument used by vaccine manufacturers against claims of serious side effects was that mRNA vaccine could not remain in the cytoplasm for a long time and no more spike protein would be produced than necessary. Accordingly, vaccine-delivered mRNA did be clearing from cells after 6-8 hours, but researchers soon disproved this argument by showing that vaccine-delivered mRNA patterns could be found in testicular and ovarian tissue even after 80 hours (34,37).
What did persistent vaccination policies mean, despite the knowledge that SARS-CoV-2 mutates very frequently?

The news of mutations and new variants that came one after another during the pandemic process caused doubts about the effectiveness of vaccines to deepen. In the study conducted by researchers at the Fred Hutchinson Institute, some mutations that impair antibody binding were detected in the parts of the host-related to the structure of the SARS-CoV-2 spike protein that binds to the ACE2 receptor (42,43). It has been announced that the effectiveness of vaccines developed against the SARS-CoV-2 spike protein may decrease as a result of these mutations. In fact, these results were one of the first studies to declare that vaccines against the SARS-CoV-2 spike protein can be thrown away. However, the first crisis was did overcome by making updated recommendations for vaccines (44).

Later, a new variant of SARS-CoV2 was detected in genetic screening studies conducted by the COVID-19 Genomics UK Consortium (COG-UK) in England (45). It was shared with the public that this new variant, called "VUI- 202012/01", which was first seen in Europe but later appeared in America, Africa, and India, is 70% more contagious (45,46). However, no data on the pathogenicity and virulence of this variant were shared with the public (44). The emergence of new SARS-CoV-2 variants has been raising concerns about vaccines. After these developments, WHO called on vaccine manufacturers and reported that COVID-19 vaccines should be updated by taking into account new variants. Soon after, the BioNTech-Pfizer joint venture announced that it has started to update the mRNA-based vaccines that are being prepared against new SARS-CoV-2 variants.

People were used to the mutation news that came up frequently. The death of tens of thousands of bison due to the detection of mutagenic forms of SARS-CoV-2 in bison in Denmark and the Netherlands brought to mind the epidemics in medieval Europe. This situation caused fear and anxiety in people. With the emergence of new SARS-CoV-2 variants almost every day, doubts about whether vaccines would be effective gave way to fear and anxiety. All these developments led to the deepening of doubts about the protective effect of vaccines from COVID-19 and the start of anti-vaccine actions.

In vaccine studies conducted in South Africa, it was determined that the COVID-19 vaccines made by Johnson & Johnson and Novavax provide weak protection against the SARS-CoV-2 variant with code B.1.351, which is responsible for the majority of SARS-CoV-2 infections in South Africa (47,48,49,50). The efficacy of these vaccines against the mild disease was 57% for J&J and 49% for Novavax, lower than in other countries where they were tested. Meanwhile, data showing that the Astra Zeneca-Oxford vaccine prepared for COVID-19 did not provide sufficient protection against the B.1.351 variant in South Africa was shared with the public (51). Thereupon, Astra Zeneca-Oxford, the vaccine project in South Africa was stopped. All these developments raised concerns about the effectiveness of vaccines on new SARS-CoV-2 variants. Subsequently, WHO again called upon vaccine manufacturers to consider new mutations and new SARS-CoV-2 variants in vaccine studies. While all these developments carried serious concerns about the effectiveness of vaccines, organized anti-vaccine social movements did was continuing in Europe and America (52).
The place of the subcontracting systems and big pharma in scientific research

What is more dangerous than COVID-19 in our time is selfishness and bigotry. Worse still is the use of science for commercial purposes in public health problems. Giving the initiative to pharmaceutical companies rather than WHO in the fight against the pandemic was an unwise practice (1). It is known from previous outbreaks and the production and marketing histories of Thalidomide and Glyphosate that Big Farma did not give good exams on public health issues. As it is known, Thalidomide is a drug that causes upper extremity anomalies in thousands of children. When Thalidomide was discovered to be a teratogen in the 1960s, the manufacturer refused to withdraw Thalidomide from the market for a long time and caused the Thalidomide disaster, which resulted in the disability of tens of thousands of children (53,54). Glyphosate is also used as a herbicide in agriculture and is held responsible for triggering many chronic diseases, especially cancer (55,56). The manufacturer continues to produce and market glyphosate despite facing numerous criminal penalties and compensation. Since this drug is used in agricultural practices in many countries of the world, it accumulates in water and soil like a toxic legacy that will make future generations sick (56).

Another issue that needs to be emphasized is the complex relationship between big pharma and research institutions. For many years, pharmaceutical companies have been supporting pharmaceutical studies that can only give them patent and license rights, which are carried out in certain research institutions. It is also thought-provoking that all of these companies, which look at their research and development studies with a purely commercial eye, have mission statements on their fancy websites that they are working for public health. Big pharma did not give a good examination during this heavy pandemic process. Global pharmaceutical companies could not develop significant projects on their own in this severe pandemic, which has claimed the lives of more than six million people and caused severe socio-economic losses. They were only able to take a role in this process by collaborating with research institutions such as BioNtec and Oxford University (1).

These big pharmaceutical companies, which presented themselves as global players in the protection of health, did not hesitate to enter into relationships of interest with politicians and bureaucrats in regulatory centers in order to further inflate their billion-dollar fund pools. They reached out to everywhere from the NIH and CDC to WHO (1). Citing the severe social and humanitarian consequences of the pandemic, vaccines were introduced to the market without waiting for licensing processes, with immediate use approvals, and whose long-term efficacy and side effects were not fully known. Vital complications that would never be tolerated under normal conditions such as thrombosis, cardiomyopathy, and brain infarctions, which are seen as side effects of these vaccines, were ignored (57,58,59). What is worse, the results of animal experiments on the efficacy and side effects of vaccines, and the reports and information on early phase studies on humans were not shared with the public. The fact that the data on the vaccines phase studies were not shared with the public increased the doubt about vaccines. This situation was a practice contrary to the right to information and the law. A lawsuit filed in the USA regarding this has resulted against vaccine manufacturers (62). With this decision, the data and related reports about the effects and side effects of vaccines
during the phase studies will be shared with the public within the framework of the right and freedom to obtain information.

Big pharma generally carries out drug and vaccine development studies by subcontracting research centers in the public or private sector. This business model, which was initiated before, continued for vaccine development studies during the COVID-19 pandemic. Pfizer firm BionTec and Astra-Zeneca also developed a vaccine project in cooperation with Oxford University. It is not correct that such a system should be established in such matters concerning public health. Big pharma's use of research institutions is open to all kinds of abuse, and it is inconvenient to apply this business model in areas that concern public health. This practice not only paved the way for unsuccessful vaccine applications in the COVID-19 pandemic but also prevented the realization of realistic projects that could be useful for ending the pandemic. Therefore, scientific research institutions need to be legally and financially autonomous and independent. It should be essential that studies be carried out independently under the umbrella of WHO, especially in matters concerning public health.

Despite the fact that COVID-19 is rarely seen in children and is not fatal, lobbying has been made to administer COVID-19 vaccines, especially mRNA vaccines, to children, and public opinion has been tried to be formed on this issue (63). As is known, although mRNA vaccines partially prevent serious disease, they cannot prevent the carrier, transmission, and spread of SARS-CoV-2 (64). In fact, there are many publications showing that mRNA vaccines increase the carrier host. In that case, why should a vaccine that does not prevent death, not reduce carrier and contagiousness, and even increasing carrier and epidemic be given to children? When there are so many doubts about the side effects of vaccines, how can these vaccines be offered to children? As a result, some members of the big pharmaceutical industry have played the NIH, CDC, and WHO into a dirty game for financial gain.

**Did mutations end the pandemic? What is Omicron telling us?**

The most feared thing was that SARS-CoV-2 mutated very frequently during the pandemic process and therefore the vaccine effectiveness was constantly decreasing. However, the thing we feared did most would be the thing that would save us. The Omicron variant, which emerged with the largest mutation seen in SARS-CoV-2, was bringing the end of the pandemic. With this major mutation, it is predicted that SARS-CoV-2 can no longer cause serious disease. Each new mutation in SARS-CoV-2 causes conformational changes in the spike protein and changes the binding strength of the spike protein to receptors on the surface of host cells, such as ACE2 (65). It is known that the binding of vaccines and antibodies to the spike protein in the Omicron variant (B.1.1.529), which emerged with the severe mutations that occurred most recently in SARS-CoV-2, is impaired, thus reducing the effectiveness of vaccines (67,68).

Mutations in the omicron caused a conformational change in the spike protein, causing the spike protein to bind twice as strongly to ACE2 receptors (67). This change was found to cause more transmission and faster spread of SARS-CoV-2. The most important change that occurred with these large-scale mutations was that Omicron actually caused a milder disease picture than the old variants (67,68). With the mutation here, it is understood that the binding
of Omicron to the host STRA6 receptors, which causes the severe disease picture, is impaired, and in this way, the severe disease picture does not develop. In fact, this is exactly the change and transformation required by the evolutionary process. In this way, the virus found its way to coexist with the host without killing the host. Evolution had done what could not be done with billions of dollars and vaccines, and the pandemic was ending on its own.

The first report on the Omicron variant came from South Africa in November-2021 (66). Initial information was that this new SARS-CoV-2 variant contained a large number of mutations and spread more rapidly than previous variants (66). This situation created an atmosphere of panic at first, alarming researchers and health authorities (66). It has been confirmed that there are 32 mutations in the Spike protein that binds to ACE-2 in Omicron, which has become the dominant form in circulation. More importantly, 15 of these mutations had been in the receptor-binding site (RBD), which is a critical site in the ACE-2 interaction of the spike protein and is considered the binding site of antibodies (67,68). Therefore, these mutations in the Omicron variant also raised great concerns about immune escape (66,67). In addition, similar mutations were found in the furin cleavage site outside the RBD, as in Omicron Alpha and Delta variants (68). These mutations in the furin cleavage site increased the infectivity of the virus, causing it to have higher fusogenic potential.

Although the Omicron variant caused panic at first because it carried the most extensive mutations seen since the beginning of the pandemic and spread rapidly, it was soon realized that it did not cause a severe clinical picture (67,68). According to a preprinted study, the reason for the increased infectivity and rapid spread of the Omicron variant is that the spike protein can bind to the host ACE2 receptors twice as strong compared to previous variants, due to the mutation occurring in the spike protein (67). In Omicron-infected patients, the infection is usually limited to the mucous membranes of the upper respiratory tract, and the lungs and intestines are not severely affected (68). Likewise, the intense expression of the ACE2 receptor in the mucous membranes of the respiratory and digestive systems supports this clinical course of Omicron. But still, Omicron can create severe clinical pictures in those who are carriers of chronic diseases that cause comorbidity for COVID-19 and in the elderly.

Meanwhile, researchers have not yet been able to explain the mechanism by which Omicron cannot create a severe disease picture. We can have clearly explained this historical evolutionary change in the pathogenesis of COVID-19 through the retinoid signaling disorder and multi-receptor mechanism (69,70,71). The explanation of retinoid signaling disorder in the pathogenesis of COVID-19 and the identification of STRA6 and GPCR receptors as strong binders of the SARS-CoV-2 spike protein by in-silico studies brought a new perspective to the pathogenesis of COVID-19 (69,71). These studies provide a clear explanation for the devastating systemic involvement and organ-specific symptoms in COVID-19. Accordingly, the conformational structure of the spike protein changes with the emerging new mutations, and the binding strength and binding status of the host cells to each of the ACE2, STRA6, and GPCR receptors change (71). Every time the binding status of the spike protein to these receptors is changed by mutations, cellular signaling pathways are also affected. In this way, clinical signs and symptoms also change in COVID-19 patients with each new variant (71).
The most important reason for the severe clinical picture in COVID-19 is retinol depletion and the resulting retinoid signaling disorder (69). In COVID-19, retinoid signaling defects may develop due to retinol depletion as well as blockade of the STRA6 receptor by spike protein (69,72). Blocking the STRA6 receptor, which is located at the junction of many cellular signaling pathways, by spike protein causes both retinoid signaling impairment and disruption of many cellular signaling pathways that operate via STRA6 and govern inflammation (72). In COVID-19, retinoid signaling defect and STRA6 receptor blockade cause disruption in Type I interferon synthesis and concomitant discharge of inflammatory cytokines (69). Therefore, the STRA6 pathway is the most important signaling pathway in the pathogenesis of COVID-19, and blocking this receptor by spike protein, as in beta and delta variants, causes severe clinical pictures in patients (72).

The large-scale mutation in the omicron and the conformational change in the receptor-binding site of the spike protein must have impaired the ability of the spike protein to bind to the host STRA6 receptor, which has a very important role in the pathogenesis of COVID-19. The fact that the STRA6 signaling pathway is not affected in patients infected with Omicron protects patients from severe clinical manifestations. We think that the signaling pathway operating via STRA6 is not involved in the pathogenesis in patients infected with Omicron, and therefore severe systemic effects and severe clinical pictures do not develop. Despite this, we think that the signaling pathways operating via ACE2 and GPCRs continue to be affected in patients infected with Omicron, but blockade in these pathways does not cause severe clinical pictures. In order to confirm this hypothesis, the interaction between the spike protein of the Omicron variant and the STRA6 receptor should be tested by molecular docking studies and compared with Beta and Delta variants.

COVID-19, chronic diseases and vitamin A deficiency: A brief epidemiological overview

One of the important things that the COVID-19 pandemic has taught us is how important a healthy diet is in maintaining our health and resisting diseases (73). It is known that unhealthy nutrition reduces our resistance to infections and causes chronic inflammatory diseases (74,75). The main reason why COVID-19 is deadly and destructive in western societies is the chronic diseases caused by this diet with high-calorie, over-processed, packaged foods that have no nutritional value (76,77,78). As it is known, the western-style diet and obesity and diabetes that develop due to it are beginning the diseases that cause comorbidity for COVID-19 (78,79,80). Meanwhile, obese individuals are also known to have lower vitamin A levels and lower vitamin A intake compared to normal-weight individuals (78). Obesity is closely associated with COVID-19, mainly due to vitamin A deficiency and the burden of inflammation (79).

Although the relationship between chronic diseases and COVID-19 has been extensively researched during the pandemic process (77), no epidemiological studies have been conducted at population scales to elucidate the relationship of COVID-19 with nutritional status and vitamin A deficiency (80). Western-style eating habits are the main cause of chronic diseases that pave the way for serious illness in COVID-19. Due to this diet, adequate amounts of vitamin A and carotenoids cannot be taken in the diet. The western diet may be a deceptive

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reason for vitamin A deficiency. In this respect, we think that a western-style diet may cause a hidden vitamin A deficiency in social scales. In vitamin, A deficiency, an increasing tendency towards infections develops, and inflammatory processes that initiate chronic disease processes are triggered (78,82,83,84,88). There are many studies in the literature that processed ready-to-eat foods trigger inflammatory mechanisms in the body and lead to chronic diseases (75,86).

Today, chronic inflammatory diseases, which are not caused by microorganisms and have become epidemics, have now become the biggest cause of mortality and morbidity in western societies (81,85). Obesity and many other chronic diseases, especially Type I and Type II diabetes, have increased significantly in western societies due to nutrition with high-calorie, packaged foods with no nutritional value and policies supporting this diet (76,80,81,82). These chronic diseases, which are becoming increasingly widespread, have become a serious health problem and an important socio-economic problem, especially for western societies (76,80,81). These chronic diseases that cause comorbidity for COVID-19 and the western-style eating habits that cause them are the main reason behind the devastating course of COVID-19 in western societies (77,78,79,80).

WHO, in its call for a healthy recovery manifesto from COVID-19, points out chronic diseases as the biggest threat to global health and high-calorie unhealthy diet as the biggest cause of them (80). In this manifesto, WHO especially emphasizes that an unhealthy diet impairs the immune defense, creating susceptibility to infections and increasing chronic diseases such as obesity and diabetes, which are the biggest risk factors for severe illness and death in COVID-19 (80). This manifesto actually means the declaration of the known. A big problem that has been known for a long time is coming back to the agenda thanks to the COVID-19 pandemic.

Despite all these facts, the lack of epidemiological studies to detect micronutrient deficiencies such as vitamin A deficiency, which predisposes to infections and chronic diseases during the pandemic process, is a major deficiency. In this process, although many studies have been conducted on the relationship between vitamin D and COVID-19, vitamin A screening has not been performed on social scales. Although there have been some studies on vitamin A, these are clinical studies for the treatment and understanding of the pathogenesis of COVID-19 (87,90,91). In these studies, it was determined that vitamin A levels were seriously reduced in COVID-19 patients. Another important finding is that it has been demonstrated that vitamin A deficiency may play a role in the development of severe disease (90,91).

It is now accepted that vitamin A deficiency is an acquired immunodeficiency picture due to micronutrient deficiency (88,89,94). Vitamin A deficiency predisposes to infections and significantly increases mortality and morbidity (89,94). Vitamin A also decreases during the course of infections (90,91,94). This bilateral interaction between vitamin A and infections creates a vicious circle in the pathogen-host interaction, increasing infection-related mortality, and morbidity (89,95). During the measles outbreaks in California, 50% of children were found to have vitamin A deficiency in screenings (95). Thereupon, WHO added the prophylactic use of vitamin A in measles to its treatment protocols. As a result, mortality rates
Measles is destructive to vitamin A metabolism and severe vitamin A deficiency occurs in the host during the course of measles (96). In the meantime, it should not be overlooked that vitamin A deficiency develops in COVID-19 and that the biggest cause of mortality is pneumonia and ARDS, as in measles. It is no coincidence that COVID-19 has hit major cities and older populations. Vitamin A deficiency is an important public health problem affecting millions of children in developing countries (97). However, this problem is not unique to third-world countries. The understanding that vitamin A deficiency is seen only in underdeveloped countries and not in developed western societies is not correct. Contrary to what is known, vitamin A deficiency can be seen at high rates in western societies. Studies conducted in Brazil and China in recent years have shown that vitamin A deficiency is high in large metropolitan areas and especially among the elderly population (98,99). Vitamin A deficiency was found at a rate of 22.01% (10.51% complete deficiency, 11.5% marginal deficiency) for elderly, metropolitan residents in the vitamin A screening performed between 2010 and 2012 in China (99). In a study in Brazil, the prevalence of vitamin A deficiency was found to be 26.1% in individuals over the age of 60 (98). These two studies clearly demonstrate that vitamin A deficiency is not unique to underdeveloped populations. The same dramatic picture is not much different in terms of vitamin D deficiency and some other micronutrient deficiencies.

In the meantime, a recent study has been published recently, showing that vitamin A deficiency is not unique to underdeveloped countries, but can also be seen in developed western societies (100). This study also emphasized the relationship between vitamin A deficiency and inflammation (100). It is significant that this study coincides with the pandemic process. Although this study is not a study on the relationship between COVID-19 and vitamin A, it is meaningful for developed western countries in terms of emphasizing the potential vitamin A deficiency. This study is also important in terms of supporting our arguments about the relationship between COVID-19 and vitamin A deficiency, albeit indirectly. The frequent and fatal course of COVID-19 in western societies, big cities, and especially in the elderly population inevitably brings to mind vitamin A deficiency. In this sense, the timing of this study, which was conducted in England, was significant.

Although the main reason for vitamin A deficiency is known as the inability to get enough vitamin A and carotenoids (provitamin A) with food (97), the factors causing vitamin A deficiency vary between societies. While the main reason for vitamin A deficiency in underdeveloped countries is malnutrition and poverty, we think that the reason for vitamin A deficiency in developed western societies is diet habits with low nutritional value, high calorie, and packaged foods. These bad eating habits are deepened by wrong, population, food, agriculture, urbanization, and health policies. Vitamin A deficiency is the main reason behind chronic diseases, which is seen as the most important reason why COVID-19 hits big metropolises more than rural areas. The relationship between vitamin A deficiency and inflammation and chronic disease has been shown in many studies (100,101,102,103). The main reason behind obesity, diabetes, cardiovascular diseases, and many other chronic inflammatory diseases that cause comorbidity for COVID-19 is nutrition with low nutritional value.
value, western style, high calorie packaged foods (104,105,106). Healthy-eating adults have a lower risk of obesity, heart disease, type 2 diabetes, and cancer, and they live longer (107). With this aspect, the fast-food style has played a role in the pandemic as the most important factor increasing mortality and morbidity in COVID-19 due to wrong/malnutrition causing comorbid diseases (106,107). This eating habit and the policies that encourage it, and the resulting increase in obesity and other chronic diseases, pose a serious threat to the health of future generations. This problem has become a heavy burden for social security institutions and state budgets due to the chronic diseases it causes (107,108).

Epidemiological scans are at the forefront of the work that needs to be done in such epidemics. These scans not only help clarify the etiopathogenesis of the disease but also identify environmental and demographic factors that may predispose to infection. It has been known for a long time that vitamin A deficiency causes susceptibility to infections (94,95,96). However, it will not be a surprise that this problem arises on the basis of chronic inflammatory diseases that increase like an epidemic and become a social wound. Likewise, many studies, including some recent studies, have deciphered the relationship between malnutrition, vitamin A deficiency, and chronic diseases (109,110,111).

The triangle of malnutrition, vitamin A deficiency, and chronic disease (inverted A triangle) has the potential to damage the socioeconomic issues of societies more severely than the pandemic in the coming years. We call this deadly triangle the inverted triangle A to create awareness and make it memorable. Figure 1 (triangle ITA). WHO, OECD, UN, and international agricultural organizations urgently need to take necessary measures for this hidden danger caused by wrong food, agriculture, and nutrition policies. The increasing chronic disease burden in urbanized western societies has become a serious threat to health and social security institutions (112,113). In COVID-19, it has been shown in several clinical studies that vitamin A deficiency causes a tendency to infection, and vitamin A deficiency develops during severe illness (90,91). COVID-19 has shown us the importance of adequate and proper nutrition. However, the vital role of vitamin A has been overlooked here. However, with chronic diseases becoming an epidemic, the importance of vitamin A will be understood once again, albeit with a bitter experience.
Meanwhile, many studies have shown that vitamin D is protective against COVID-19 and prevents severe disease (114,115,116). Meanwhile, vitamin D, which, like vitamin A, acts through the retinoid signaling mechanism, is a good immune modulator and also shows protective activity against chronic inflammatory diseases (117,118). Epidemiological studies have shown that 25-OHD (vitD) deficiency is closely associated with common chronic diseases such as bone metabolic disorders, tumors, cardiovascular diseases, and diabetes. VitD deficiency is also a risk factor for neuropsychiatric disorders and autoimmune diseases (119,120,121).

Despite all these facts, unfortunately, no vitamin A screening was carried out on social scales during the pandemic process. In this way, we missed the chance to use vitamin A, which is very common in the world and very cheap, to control the COVID-19 pandemic. Vitamin A has the power to create a socio-economic multiplier effect on global scales, due to its potential to protect millions of patients from chronic diseases. In this sense, recently from the London School of Economics, Dr. It is significant that Daniele Fanelli and her team have launched an initiative to incentive the global use of vitamin D against COVID-19 (122). This initiative, supported by many scientists, calls on health authorities to use vitamin D against COVID-19 (122). This attempt to control the pandemic, unfortunately, coincided with the end of the pandemic. Although this is a missed opportunity for COVID-19, the prophylactic use of vitamins A and D on a global scale can be of great benefit in controlling chronic diseases. In this respect, this project initiated by Fanelli should not be limited to COVID-19 and should be applied specifically to prevent chronic diseases (122). The implementation and maintenance
of this project are very important in terms of preventing chronic diseases that are on the eve of a serious socio-economic crisis.

In fact, epidemiological screening is the first thing to be done in epidemics. These scans provide both to clarify the etiopathogenesis of the disease and to detect environmental and demographic reasons such as nutritional habits that may predispose to infection. Although some studies have been conducted on the population-based dynamics of the spread of COVID-19 and the relationship between COVID-19 and vitamin D, no significant study has been conducted on vitamin A deficiency, which may be effective in the spread of COVID-19 and the formation of severe disease. The few clinical studies that have been conducted are also far from determining the real causes underlying the geographical and demographic distribution of COVID-19.

**Conclusion**

It is understood from the panic and confusion experienced during the pandemic process that health authorities and governments were caught unprepared for the pandemic. The lack of organization that emerged in this process, the interest relations between pharmaceutical companies, politicians, and research centers, and the restriction of people's freedoms were developments that will go down in world history and learn from. Restricting the ordinary course of daily life, travel, education, trade for two years, and making all life activities, including education and social life, conditional on vaccination, and the introduction of vaccination passports by governments were practices that restricted basic human right freedoms. For this purpose, it is clear that human rights and freedoms have been seriously violated throughout the world. It will never be forgotten that the digital technology developed to facilitate human life is transformed into an electronic handcuff to follow people and used for this purpose.

The elimination of all doubts in the pandemic process is very important in terms of being able to fight the epidemics that may arise in the coming years and to build the future accordingly. In a possible future pandemic, WHO should not leave the health of millions of people at the mercy of commercial establishments. For this purpose, it is obvious that the organizational chart within WHO should be restructured in order for governments to support WHO's financial and institutional infrastructure and to be prepared for possible disasters and pandemics. In addition, autonomous and independent research institutions must be established as soon as possible so that medical research can be carried out freely and impartially.

The pandemic did not end with vaccines turned into an economic rent war. The pandemic ends by turning into a simple flu infection with a heavy mutation of the virus as required by the evolutionary process. But with a dozen chronic residual diseases and gene transfer vaccines applied for the first time in history, it ends on its own, leaving serious doubts behind it. On the other hand, the disruption of social life, travel, education, production, and trade for a simple flu infection that caused a pandemic created a domino effect and caused the biggest socioeconomic crisis after the Second World War. Did the measures take to prevent the spread of the epidemic hurt us more than the epidemic itself?
Metaflammation, which occurs as a result of Western-style nutrition, causes the development of chronic diseases that is not contagious but spread like an epidemic. These pathologies related to nutrition and lifestyle represent a public health problem that is rising with the dimensions of global epidemics. These diseases, in addition to being traumatic for individuals and families, have also become a heavy burden for states in social security mechanisms and state budgets. In this respect, the wrongly constructed food, agriculture, nutrition, environment, population, urbanization, medicine, and health policies should be reviewed and rearranged accordingly. It is necessary to make radical changes in the wrong policies applied especially in the field of food, agriculture, medicine, and nutrition. We hope that the process that COVID-19 has caused staggering changes in the health system and many other areas of life has taught us a lesson from this perspective as well. In this respect, healthy life and healthy nutrition will be our most important issues in the coming years. This trend will also be reflected in the food, agriculture, pharmaceutical, and health policies.

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