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NEW PERSPECTIVES

Chronic pain in post-COVID syndrome

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ABSTRACT
Our body senses two types of pain, acute and chronic. Acute pain lasts for a short time. It occurs when our body wants to protect us from a dangerous situation. This way, our nerves are telling us that something is wrong. But if some time passes since our injury, treatment or surgery and the pain or discomfort persists, we are speaking of chronic pain. It is often difficult to determine its intensity or even prove its existence. The discomfort and pain are not relieved and physical pain may be accompanied by mental issues. At present, during the COVID-19 pandemic, chronic pain is becoming more prominent, and it is also associated with the post-COVID syndrome. In their efforts to help patients suffering from COVID-19, many new treatment protocols have been prepared and various antiviral drugs and other potentially useful drugs have been used (often without prior approval or testing). Basically, it was a kind of 'experimental' treatment. At present, thanks to quick therapy decisions and as part of COVID-19 prevention, we have succeeded in stabilising the situation all over the world. A relatively fast development of vaccines against SARS-CoV-2 with a view to achieve collective immunity has greatly contributed to this. On the other hand, 'quick decisions' have contributed to other significant issues which we are beginning to deal with now, i.e, in the effort to defeat the virus, many experts regarded the adverse effects of the medications used to be of secondary importance. In the article we would like to point out the other side of the 'successful' treatment of COVID-19, namely the possible iatrogenic conditions which significantly contribute to the post-COVID-19 syndrome and chronic pain. The importance of preventive measures over uncertain result of COVID-19 treatment is emphasised *(Tab. 4, Fig. 1, Ref. 50)*. Text in PDF *www.elis.sk*
KEY WORDS**:** iatrogenic conditions; chronic pain; co-morbidity; pain syndrome; pandemic; post-COVID-19 syndrome.

Introduction

COVID-19 was officially registered by the World Health Organization (WHO) on 31 December 2019, when the Ministry of Health of the People's Republic of China reported 44 cases of SARS in the city of Wuhan in the Hubei Province. It was discovered that COVID-19 is caused by the new coronavirus SARS-CoV-2. On 11 March 2020, the WHO declared the spread of COVID-19 to be a pandemic (1–3). The danger of COVID-19 infection lies in its higher transmission rate (several times higher than in the case of flu) and long incubation period (up to 14 days), which is further complicated by the fact that asymptomatic patients may also spread the infection. COVID-19 can have a severe course, in particular in patients with underlying chronic illness (3).

These characteristics of COVID-19 place increased demands on the organisation of the healthcare system. An especially high transmission rate is currently the reason why so many people worldwide contract COVID-19. This has led to an excess burden on healthcare systems in many countries. The severe course of infection (in particular with affected lungs) in patients with chronic pathology very often requires the use of mechanical lung ventilation (MLV) and is associated with high mortality rate (2, 3).

It is assumed that the ability to slow down the spread of the coronavirus infection is currently the most important preventive measure, which would result in decreased hospital admissions and reduced burden on healthcare facilities. However, the attempts to fight the coronavirus infection merely by using quarantine measures (wearing masks, gloves, hand sanitation and washing, restriction of social contacts, isolation, etc.) have nothing do to with the most important source of prevention, i.e, the activation of intrinsic antiviral immune systems (3). Important in the process of activating antiviral immunity (linked to interferon synthesis) in

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the prevention of COVID-19 is in particular the improvement in vitamin D levels and use of other micronutrients. Vaccination is also extremely important in COVID-19 prevention. Vaccination aims to achieve collective immunity which will result in gradual elimination of the virus from the worldwide population (4, 5).

The purpose of the article is to demonstrate the side effects of treatment with various drugs (and their combinations) that are used to treat COVID-19 disease. We also focus on the benefits and relative safety of vaccination.

Current strategy of COVID-19 treatment

When COVID-19 (with affected lungs in particular) is treated with medications, it is very important to prevent the development of 'the cytokine storm', which can be characterised as an avalanche-like increase in the concentration of proinflammatory cytokines resulting in lung damage and hypoxia (6, 7). This condition requires oxygen therapy (treatment using oxygen or mechanical lung ventilation). By affecting 'the cytokine storm', it is possible to reduce the mortality of COVID-19 patients (3). The presence of another disease (atherosclerosis, obesity, diabetes mellitus, bronchial asthma, arterial hypertension, etc.) in these patients supports and accelerates the synthesis of proinflammatory cytokines, including interleukin-1, chemokine CCL2, interleukin-6 and interferon-gamma. Interleukins increase activation of leukocytes and breakdown of mast cell granules (3, 5).

Stabilisation of accompanying chronic co-morbidities is very important for the treatment strategy and prevention of COVID-19 given that the presence of complications like cardiomyopathy, thrombotic embolism, obesity, arterial hypertension, coronary artery disease and diabetes mellitus in patients is associated with a risk of more severe course of the disease (3, 5, 6). Treatment protocols for this new disease are constantly changing and new options of treatment and prevention are emerging (Fig. 1) (5, 6). The figure shows new possibilities for the treatment of COVID-19 disease (such as serum therapy, mAb therapy, adoptive immunotherapy, mesenchymal stromal cells, anti-viral drugs, decoy biomolecules, nanomedicine).

From the beginning of January until mid-May, the COVID-19 Department of the 2nd Surgical Clinic of the Faculty of Medicine of the Comenius University in Bratislava (University Hospital Bratislava, Hospital of Saints Cyril and Methodius) treated 221 patients with moderate-to-severe and severe course of COVID-19 (2nd wave of the pandemic).

In February 2021, the mortality rate at our department reached 33 %, with a third of patients requiring high-flow oxygen therapy. During this period, Slovakia became the worst in the world in terms of the number of deaths and hospitalised cases per capita. The treatment was often complicated by co-morbidities, which worsened the disease course. We also saw some adverse effects and lack of effect of certain drugs for COVID-19. Some of the drugs could not be used due to various contraindications and interactions with other drugs (chronic treatment), etc. We also had 5.8 % of bleeding cases associated with the use of anticoagulant therapy (as part of antiviral therapy), particularly in combination with preparations from the group of Janus kinase inhibitors.

Drug therapy of COVID-19, adverse effects of drugs

The worldwide opinions on the treatment and prevention of the disease differ. An increasing number of sites prefer therapy recommended by Front Line COVID-19 Critical Care Alliance under the leadership of the world-renowned expert on intensive care medicine, Doctor Paul Marik from the USA, who counts among the world's most published scientists. Together with his team, they created a so-called 'MATH+' protocol for the treatment of hospitalised patients and 'I-MASK+' protocol for prevention and early treatment in an outpatient setting (8, 9). Protocols are constantly updated as new knowledge emerges. Treatment success also depends on good timing since the lungs are affected starting from the 5th day of a non-improving condition and it is inevitable to initiate complex anti-inflammatory and anti-coagulant therapy according to the hospital protocol as early as possible. Otherwise, the lungs become even more affected, complications develop, and it may be too late.

In any event, COVID-19 treatment is complicated and includes 'a cocktail of medications' which are not always helpful and even have the potential to harm patients (10). By the adverse effect of a drug, we mean any harmful and undesired reaction which occurs with common therapeutic or preventive doses of the drug. It is usually mild in nature and disappears after with-

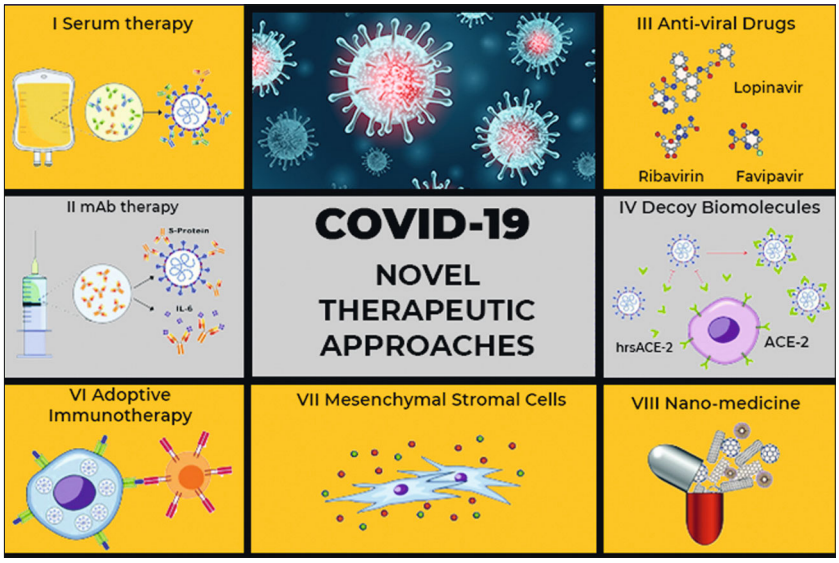

Fig. 1. New treatment options for COVID-19. Source: adapted by the authors according to various sources of literature (5, 6).

Tab. 1. Adverse effects of corticosteroids.

Infections and infestations	Masking of infections, signs and exacerbations of viral, fungal, bacterial, parasitic and opportunistic infections, activation of strongyloidiasis.
Blood and lymphatic system disorders	Moderate leucocytosis, lymphocytopenia, eosinopenia, polycythaemia.
Immune system disorders	Hypersensitivity reactions (e.g, rash after medication): moderate anaphylactic reactions, such as arrhythmia, bronchospasm, hypotension or hypertension, circulatory system failure, cardiac arrest, weakening of the immune system.
Endocrine disorders	Adrenal gland suppression and development of Cushing syndrome (typical signs: moon face, abdominal obesity, and plethora).
Metabolism and nutrition disorders	Sodium retention with oedema, increased elimination of potassium (risk of arrhythmia): body weight gain, reduced glucose tolerance, diabetes mellitus, hypercholesterolemia and hypertriglyceridemia, increased appetite.
Psychiatric disorders	Depression, irritability, euphoria, increased activity, psychoses, mania, hallucinations, emotional lability, anxiety, sleep disorders, suicidal tendencies.
Nervous system disorders	Pseudotumor cerebri, manifestation of latent epilepsy, increased number of seizures in obvious epilepsy.
Eye disorders	Cataract, in particular with posterior subcapsular opacification, glaucoma, worsened symptoms of corneal ulcers, increased incidence of viral and fungal eye disorders, worsened bacterial inflammation of the cornea, ptosis, mydriasis, chemosis, iatrogenic scleral perforation, chorioretinopathy, blurred vision (see also section 4.4).
Vascular disorders	Hypertension, increased risk of atherosclerosis and risk of thrombosis, vasculitis (also as a symptom of withdrawal in case of long-term treatment): increased capillary fragility.
Gastrointestinal disorders	Gastrointestinal ulcers, gastrointestinal bleeding, pancreatitis, stomach pain, urination.
Skin and subcutaneous tissue disorders	Striae, atrophy, telangiectasia, petechiae, ecchymosis, hypertrichosis, steroid acne, perioral dermatitis, pigment disorders.
Musculoskeletal and connective tissue disorders	Myopathy, muscular atrophy and weakness, osteoporosis (dose-dependent, also possible in the case of short-term treatment): aseptic bone necrosis, tendon disorders, tendinitis, tendon rupture, epidural lipomatosis, growth inhibition in children.
Reproductive system and breast disorders	Impaired elimination of sex hormones (with subsequent irregular periods to amenorrhea, hirsutism, impotence).
General disorders and administration site conditions	Prolonged wound healing.

Source: adapted by the authors according to various sources of literature (13, 15, 16).

drawal of the drug. It does not necessarily occur in every patient. Patients can find information on adverse effects in the patient information leaflet. We distinguish between serious (life-threatening, requiring hospitalisation) and less serious adverse effects of drugs (conditions that can be managed at home).

In terms of risk (frequency), the adverse effects are divided into very common, common, uncommon, rare, and very rare. If an adverse effect is very common, it means that more than 100 patients in 1,000 may develop it. A common adverse effect is developed by 10-100 patients out of 1,000 and uncommon in 1–10 people out of 1,000. If an adverse effect occurs in less than 1 person in 1,000, we speak of a rare effect. If it occurs even more rarely, it is a very rare side effect (11).

Below are some of the most commonly used drugs for COVID-19 and their most significant adverse effects.

Corticosteroid drugs have been a subject of various studies, including the Recovery study which validated its efficacy and brought excellent news (12). Dexamethasone cannot treat COVID-19, but as has been mentioned, it effectively reduces the massive inflammation that develops in this disease and causes many deaths (13, 14). The WHO (World Health Organization) issues guidelines on the treatment of various diseases. Dexamethasone has been included in the guideline on the treatment of COVID-19. It is cheap, available, and effective in saving many lives. Guidelines recommend using an intravenous or tablet form of the corticosteroid therapy with dexamethasone in patients with severe course of the disease (13, 14).

Prevention of complications is always better than their later management. When immunity is suppressed with corticosteroids, no cytokine storm occurs, but our body is weakened in the fight against the virus itself. For this reason, the therapy should only be administered to patients with a severe course of the disease, since in cases of a milder course, corticosteroids would do more harm than good. Actually, no improvements have been seen in patients with milder course of the disease. The adverse effects of corticosteroids (Tab. 1) may develop, depending on the dosage and duration of the treatment, which means that the frequency of their occurrence cannot be established (13, 15, 16).

Antiviral agents (remdesivir, lopinavir-ritonavir, hydroxychloroquine, tocilizumab) were also tested in the previous months (originally against Ebola, malaria and AIDS) with high expectations of scientists. Unfortunately, it turned out that they have no impact on the mortality of COVID-19-positive patients. The WHO study also did not demonstrate their effect on shortening the hospitalisation or mechanical lung ventilation therapy (17–19). Side effects of antiviral drugs are listed in Table 2 (17–19).

Plasma is a pale-yellow fluid that represents the liquid part of the blood and helps ‘distribute’ blood cells in the body. It con-

Tab. 2. Adverse effects of many antiviral agents.

Frequency	Adverse reaction
Immune system disorders	
Rare	Hypersensitivity
Unknown	Anaphylactic reaction
Nervous system disorders	
Common	Headache
Cardiac disorders	
Unknown	Sinus bradycardia
Gastrointestinal disorders	
Common	Nausea
Hepatobiliary disorders	
Very common	Increased transaminase levels
Skin and subcutaneous tissue disorders	
Common	Rash
Laboratory and additional examinations	
Very common	Prolonged prothrombin time
Injuries, poisonings and procedural complications	
Rare	Infusion-related reaction

Source: adapted by the authors according to various sources of literature (17–19).

sists mainly of water (90–92 %), the rest of its volume consists of proteins (8 %) and inorganic substances (1 %) (20, 21). When a person comes into contact with some foreign substance (virus, bacterium, etc.), the human body produces antibodies against the substance and saves them 'for bad times'. It means that when it encounters the foreign substance again, it will be ready for it. Basically, antibodies are a type of proteins contained in the plasma, which is why scientists came up with the idea of plasma therapy. A patient with COVID-19 is given the plasma of another patient who has overcome the coronavirus infection and recovered, i.e, his/her plasma contains antibodies which may help the patient in the early stages of therapy. The solution is almost painless and has no side effects.

The risk of plasma administration, adverse effects (20, 21):

- volume overload in the case of fast infusion rate and high plasma volume (TACO – transfusion-associated circulatory overload), in particular in patients with cardiac risk factors, risk of heart failure and lung oedema,
- citrate intoxication in the case of fast infusion rate and high plasma volume, in particular in the case of liver failure, shock, acidosis and hypothermia,
- allergic reactions, in rare cases anaphylactic shock,
- risk of transfusion-transmitted infection agents such as bacteria, viruses (HIV, HCV, HBV, CMV) and others,
- acute lung injury associated with transfusion (TRALI – transfusion-associated lung injury).

In line with the hospital treatment protocol, low molecular weight heparin (LMWH) is often used since COVID-19 causes a hypercoagulable state (19). As of 6 November 2020, Aspirin became subject to the largest clinical study examining treatment options for patients hospitalised with COVID-19 (12). This widely available and well-known drug has its place in the first aid kit in almost every household.

Aspirin has antipyretic (reducing fever), analgetic (reducing pain), antiphlogistic (suppressing inflammation) and anticoagulation (against blood coagulation) effects. All of them could be helpful in the treatment of COVID-19, but the research is currently focusing on the latter one, i.e, on the anticoagulation effect (5, 12, 19). The potential life-threatening complications of COVID-19 include blood clots (thrombi). This is due to blood platelets responsible for coagulation (clotting) of blood which are hyperactive in this disease. Adverse effects of anticoagulation therapy include bleeding in case of overdose, allergic reaction, thrombocytopenia, potential osteoporosis, and bruising.

Vitamin D, which is present in three forms in the body, also helps to regulate the cytokine storm in a natural way. One of those forms is calcifediol (25-hydroxyvitamin D3), the concentration of which is also determined when testing for the amount of vitamin D in the blood. When calcifediol is supplemented, the body can absorb it easily and its concentration in the blood increases rapidly (22). These characteristics were one of the reasons why Spanish scientists have chosen this form of the vitamin for their pilot clinical study.

The research included 76 patients with COVID-19, all receiving best available treatment. In addition, 50 patients received calcifediol. As a result, only one person required intensive care and none of the patients died. Of the remaining 26 patients (control) who did not receive calcifediol, as many as 13 (50 %) ended up in the ICU (intensive care unit) and 2 patients died (12).

The results are significant and indicate that the administration of vitamin D in this form can alleviate the course of the disease and significantly reduce the number of patients requiring intensive care. However, given that the study did not include patient risk factors, such as obesity, high blood pressure or diabetes that complicate the course of COVID-19, this matter needs to be explored further (with a larger, better comparable sample), (3, 12, 22). In any case, vitamin D plays a significant role in the proper functioning of our immune system and its sufficient blood concentrations influence the course of COVID-19. Adverse effects of vitamin D supplementation include hypercalcemia and hypercalciuria, pruritus, rash and urticaria (uncommon) (23–25).

Several relevant clinical investigations have shown that vitamin C effectively shortens the period of viral infections. Since COVID-19 is one of the viral diseases, professionals assume that it is desirable to apply vitamin C at the time of active coronavirus disease (26). It is estimated that the infectious disease is shortened by up to 8 % in adults and 14 % in children (12, 26). Even though the benefits of vitamin C for the body are widely known, the coronavirus infection is new wherefore there are yet not enough relevant scientific studies to confirm the effect of taking vitamin C-containing products during COVID-19. There are even cases of acute renal insufficiency caused by high doses of vitamin C (27, 28).

Antibiotic treatment is very common and effective, however only in case of bacterial infections. Since COVID-19 is caused by a virus, antibiotics are not effective against it. In the case of coronavirus, antibiotics are administered only when there is a risk that the patient (due to weakening of the organism) develops com-

Tab. 3. Adverse effects of antibiotics (most common/general).

Adverse effects of antibiotics (most common/general)
Allergic manifestations
● Biological effects (in particular broad-spectrum antibiotics):
* They affect the microbiome → dysbiosis:
* Gut dysbiosis – vitamin K deficit, diarrhoea, Cl. Difficile infections
* Vaginal dysbiosis, vaginosis, vaginal candidiasis
* Oral candidiasis Bacterial superinfection with resistant strains
● Toxic effects: often dose-dependent
● Cumulative, e.g, nephrotoxicity, neurotoxicity, hepatotoxicity, phototoxicity, damage to growth cartilage

Source: adapted by the authors according to various sources of literature (29–32).

plications in form of an accompanying bacterial infection. This is most common in hospitalised patients with a more severe form of the disease (29, 30). Some side effects of antibiotic drugs are listed in Table 3 (29–32).

Fluoroquinolone antibiotics are often used to treat secondary infections during COVID-19 and may result in severe chronic complications (33). They are antibacterial drugs that came into use around 1987. At first, they were reserved for the treatment of the most severe infections, but soon became effectively safe, and cheap and therefore commonly used. It took more than 20 years to discover that their safety it not as ideal as previously assumed. Apart from skin manifestations, headaches and dizziness, fluoroquinolones may rarely cause severe damage to the nervous system. There is also the possibility of damage to the musculoskeletal system (e.g, tendon damage, even rupture of the Achilles tendon, mostly in the elderly) occuring in particular with higher total doses (34, 35).

Due to a certain degree of teratogenicity and adverse effect on the development of joint cartilage, its administration is usually not recommended to pregnant and breastfeeding women and children, except for severe, otherwise untreatable infections. In addition to various non-significant and transient health issues, fluoroquinolones may also cause heart rhythm disorders that in unique cases might be life-threatening. On 12 May 2016, the European Medicines Agency (EMA) finally published the opinion that due to the risk of potential permanent damage to health, patients with uncomplicated infectious diseases should not be treated with this group of antibiotics if there are other treatment options available. This is true, in particular, in case of patients with non-significant respiratory and urinary infections as has already been mentioned (36).

Adverse effects of vaccines

Vaccines for the prevention of COVID-19 are administered intramuscularly and may cause reactions within hours or even days after administration. Reported suspected adverse effects are usual and in accordance with the already known adverse effects listed in the medicinal product dossier (Tab. 4) (37–40). The most often reported adverse reactions are short-term and non-serious (40). They include, for example, injection site pain which may develop into pain in the arm and extremity to which the vaccine was administered, increased temperature, chills, shivering, headache, muscle and joint pain, weakness, fatigue, nausea and others. Such reactions are mild to moderate in intensity and resolve within a few days of vaccine administration.

The safety profile of vaccines used for the prevention of COVID-19 is reviewed on a monthly basis at local levels and at that of the European Union. At the European Union level, the safety profile of registered vaccines has been shown to be largely in accordance with the drug dossier and the benefits of the vaccine far outweigh any potential risks. In addition to symptomatic treatment, patients with a more severe course of the disease require hospitalisation, supportive oxygen therapy (administration of oxygen), and cases that are even more severe than that must be put on mechanical lung ventilation (MLV) (41–43).

Adverse effects of MLVinclude ventilator pneumonia, nosocomial infections, patient airway damage (due to long-term pressure by the tracheal cannula, insufficiently or excessively moisturised mixture of inhaled gases or excess oxygen concentration in the inhaled mixture), lung injury due to excess pressure, VILI (ventilator-induced lung Injury) or lung injury associated with ventilation, pneumothorax, emphysema, lung oedema, and other conditions (43–45).

Adverse effects of oxygen therapy include lung injury (oxygen toxicity due to its high concentration can lead to ARDS, chronic

Tab. 4. Adverse effects of the vaccine vs. consequences of COVID-19.

Long-term (side) effects	
Vaccine	COVID-19
All adverse effects specified in the patient information leaflet are short-term in nature.	Some people have long-term symptoms even after recovery.
Long-term side effects of vaccines are rare.	76% of patients (Lancet) had persisting signs even 6 months after recovery
None of the vaccines registered in the EU later had their registration withdrawn due to side effects that develop later.	56% of patients (Australian study) had damaged lungs even three months after dismissal from hospital.
Various vaccines are tested on volunteers for the last three years, with no known case of long-term side effects.	For the time being it is not completely clear how long the consequences of COVID-19 might persist and whether they will be permanent in some cases.

Source: adapted by the authors according to various sources of literature (37–40).

lung fibrosis, emphysema**)**, damage to the CNS (rate of progression is directly proportional to the partial pressure) causing impaired vision (tunnel vision), tinnitus, nausea, mimic muscle jerks, dizziness, confusion (the picture is variable) → tonic-clonic spasm, impaired consciousness, eyesight damage caused by hyperoxic myopia, retinopathy, damage to other organs caused by erythrocyte destruction, damage to the myocardium, endocrine glands (adrenal glands, gonads and thyroid gland) and kidneys (46–50).

Conclusions

Currently, all treatment protocols include corticoids, antiviral agents, vitamins, medications to stabilise underlying and accompanying co-morbidities and antibiotics. The benefits of preventive measures compared to this 'treatment cocktail' are enormous. For example, corticoids can impair metabolism, cause diabetes, or suppress immunity. Antibiotics, on the other hand, may cause colitis while blood pressure medications may negatively impact blood circulation. Moreover, we do not even know whether these drugs will help a patient recover from their severe condition in case they avoided the vaccine (and other preventive measures) and later arrived at the intensive care unit in a severe condition. Therefore, preventive measures such as vaccination and activation of intrinsic antiviral immune systems are based on an incomparable benefit. Hence, that is why one should not rely on treatment with uncertain result.

Vaccination is an effective means of combatting the SARS-CoV-2 virus which has caused the pandemic that paralysed entire countries, families, communities, and individuals worldwide. Scientific authorities and historical facts clearly show that the most efficient way of defeating any virus is the use of a safe and effective vaccine. Vaccination against COVID-19 protects not only the particular individuals being vaccinated, but also affords collective protection to the community and society as a whole. A vaccinated person is less likely to spread the infectious disease to other persons. It means that vaccination can help protect those who cannot receive the vaccine.

To ensure the so-called collective immunity on a national level in case of COVID-19, it is necessary to vaccinate more than 60–70 % of the population. Vaccination is essential for saving lives, but it will not end the pandemic overnight. Therefore, we must use other forms of prevention. In the process of activating antiviral immunity (linked to the synthesis of interferon), supplementing vitamin D and other micronutrients is particularly important in preventing the 'cytokine storm' and compensating chronic concomitant diseases.

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