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The consequences of the COVID-19 pandemic among hemodialysis patients

Abstract

The outbreak of the COVID-19 pandemic in late 2019 and early 2020 came abruptly causing a significant challenge to the entire world. The number of infections and deaths reached unprecedented levels. Among the most vulnerable to infection and death were patients undergoing chronic hemodialysis, who, on one hand, could not limit their social interactions, and on the other hand, were burdened with numerous coexisting diseases and exhibited compromised immune systems. The development of the first vaccines and the prioritized vaccination against COVID-19 for almost the entire dialysis population saved thousands of patients. The pandemic period, despite its immense tragedy, offers valuable lessons for the future, both in terms of established response strategies and temporary precautionary measures, as well as in reinforcing the conviction of how effective vaccinations are in overcoming infectious diseases, especially in a population as vulnerable as dialysis patients. In this paper, we summarize this challenging period, largely based on our own research conducted at the dialysis center in Gdansk.

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Key words: COVID-19, SARS-CoV-2, chronic kidney disease, hemodialysis

CHRONIC KIDNEY DISEASE AND ITS CONSEQUENCES

Chronic kidney disease (CKD) is a civilization-related health issue in the modern world, posing a significant global medical challenge. According to recent reports, more than 840 million people are affected by CKD, accounting for over 10% of the world's population. In Poland, this condition may afflict over 4 million individuals. Notably, CKD can remain asymptomatic not only in its early stages but even in more advanced stages of the disease. Consequently, a substantial portion of affected individuals may not be aware of their condition. Furthermore, patients with CKD often have other comorbidities, including hypertension, diabetes, and ischemic heart disease [1]. Approximately 1–2% of patients experience a gradual progression of CKD to end-stage renal failure. At that point renal replacement therapy through dialysis or kidney transplantation is needed. As of the end of 2022, there were a total of 20,198 dialysis patients in Poland, with 19,389 undergoing repeated hemodialysis (HD) treatments [2, 3].

THE DISTINCTIVENESS OF HEMODIALYSIS PATIENTS

Patients undergoing repeated HD are typically older individuals with multiple comorbidities, a high frailty index, and limited physical functioning. The underlying disease, impaired excretory and secretory renal function, chronic inflammation, and oxidative stress that develops in these patients as the disease progresses all lead to the impairment of various mechanisms of natural and acquired immune responses. This results in an increased susceptibility to various infections, which are the second most common cause of morbidity and mortality (after cardiovascular diseases) in this patient group, accounting for approximately 30–36% of deaths. For example, the risk of death due to sepsis among HD patients is approximately 250 times higher than in the general population [4–7].

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COVID-19 PANDEMIC

The consequences of the Coronavirus disease 2019 (COVID-19) pandemic among HD patients serve as a vivid example of the problem mentioned earlier. The first reports of an unexplained, previously unseen syndrome of symptomatic respiratory failure came from the Chinese city of Wuhan in the second half of December 2019, which was recognized as the epicenter of the future pandemic [8]. Ongoing globalization created a broad pathway for the spread of the infection worldwide. The first case of COVID-19 in the USA appeared on January 20, and in Europe on January 24, 2020 [9, 10]. On March 11, 2020, the World Health Organization (WHO) declared a pandemic in response to the rapid global increase in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infections worldwide, leading to severe acute respiratory failure syndrome named COVID-19.

The etiological factor causing COVID-19 symptoms, which were predominantly cough, shortness of breath, fever, and loss of taste, was identified and sequenced in January 2020 [11]. It was found to be a positive-sense single-stranded RNA virus belonging to the Coronaviridae family. It is genetically related to the MERS and SARS-CoV-1 viruses that caused epidemics in the early 2000s, but compared to them, it exhibits greater contagiousness and lower virulence [12]. SARS-CoV-2 is transmitted between people via respiratory droplets when an infected person comes into contact with a susceptible individual's saliva or respiratory secretions. Structurally, SARS-CoV-2 consists of four structural proteins: envelope protein (E), membrane protein (M), nucleocapsid protein (N), and spike protein (S). Protein N surrounds the virus's RNA, while the other proteins (S, M, E) are involved in creating the viral envelope. The spike protein, especially important in host cell invasion, has two subunits, S1 and S2, which mediate the critical steps in this process, such as attachment to the host cell membrane and fusion with its surface [13]. The receptor to which the spike protein binds is ACE2, a membrane form of angiotensin-converting enzyme 2, an enzyme involved in the renin-angiotensin-aldosterone system (RAAS). In this system, it converts angiotensin 1–9 into angiotensin 1–7. ACE2 is present in the respiratory tract, kidneys, intestines, and the heart [14]. The presence of the receptor in these locations correlates with both high adsorption of airborne virus particles (in the case of respiratory tract localization) and the occurrence of short-term and long-term complications of the infection (in other locations) [13]. Since the beginning of the pandemic, numerous mutations occurred in the genetic material of the original version of the SARS-CoV-2 virus, particularly in the genes coding for the spike protein. These mutations led to the emergence of new virus variants [15]. These variants differed in terms of contagiousness, virulence, and resistance. Currently, there are hundreds of different virus variants known, and the most important from a prognostic point of view are the so-called "Variants of Concern" (VOC) — genetic variants associated with a higher risk of severe infection and death [16].

MORTALITY DUE TO COVID-19

The COVID-19 fatality rate among the Polish population in March 2020 was 2.94%, gradually decreasing and reaching a percentage of 1.83% as of October 25, 2023 [17]. This rate is significantly lower than those observed during SARS and MERS infections, which were 9.5% and 34.4%, respectively [18]. As of October 28, 2023, there have been 771,549,718 confirmed cases of the disease, including 6,974,473 cases of death due to COVID-19 [19]. According to data presented by the Polish Ministry of Health as of October 28, 2023, the number of confirmed COVID-19 infections in Poland since the beginning of the pandemic was 6,532,844, with 119,685 deaths [20].

COVID-19 AMONG HD PATIENTS

The period of the COVID-19 pandemic had a multifaceted impact on the lives of dialysis patients. It left a devastating mark in the form of high mortality rate, especially in the period before the introduction of population-wide vaccinations, as well as in the distant consequences taking the form of post-COVID-19 syndrome. It also served as an experimental field for medical personnel dealing with this group of patients in terms of conducting dialysis during the pandemic, primarily focusing on measures to prevent the spread of the virus among patients and staff [21].

Patients with CKD turned out to be one of the groups most vulnerable to contracting COVID-19, experiencing a severe course of the

disease and a high risk of death due to COVID--19 infection. The risk increased with the degree of kidney function impairment, reaching its highest level among patients treated with HD [22]. The necessity of undergoing dialysis procedures three times a week made it impossible for patients to isolate themselves. They had to interact with drivers, other patients, and dialysis center Staff, which identified them as individuals at high risk of contracting COVID-19. In a multicenter study conducted in the Pomeranian Voivodeship, analyzing the incidence and mortality due to COVID-19, Puchalska et al. [23] demonstrated that the absolute cumulative incidence of COVID-19 from the beginning of the pandemic to the start of the national vaccination program was nearly four times higher in HD patients than in the general population of the Pomeranian Voivodeship, amounting to 22.4%. It is worth noting that this difference may have been slightly overestimated due to the fact that in some dialysis centers, screening tests were conducted on all patients or those who had contact with individuals confirmed to be infected with SARS-CoV-2, which was not commonly performed in the general population. As shown in data published in annual reports on the state of renal replacement therapy in Poland, in the years 2020, 2021, and 2022, COVID-19 affected 21%, 16%, and 18% of all dialysis patients, respectively [3, 24, 25]. Comparing the incidence of COVID-19 with other countries and dialysis centers is very difficult. Since the beginning of the epidemic, various actions to limit the spread of the virus have been implemented by dialysis centers and the incidence of COVID-19 in different units differed significantly. Moreover, the spread of the virus was undoubtedly also influenced by the epidemiological policies introduced by the governments of individual countries, e.g. lockdown during the first and second waves of infections. Additionally, any comparison is made difficult by the fact that nearly 50% of cases may have been asymptomatic [26].

The manifestations of COVID-19 changed during the pandemic with the evolution of the virus and its variants, as well as with the introduction of vaccination. Variants differed not only in the structure and course of the disease caused, but also in the degree of infectivity. The symptomatology did not differ significantly from that of the general population. The most common early clinical symptoms at admission included fatigue, fever, dyspnea, and cough [27–29]. Observations made at center in Gdansk showed that the clinical course of the disease in HD patients was insidious, yet rapid and severe. At the time of diagnosis, nearly one-third of patients had no symptoms, and a large portion reported single symptoms, much less frequently than in the general population. This is understandable given the numerous immune disorders and impaired reactivity in the group with CKD. On the other hand, as many as 20% of patients had reduced blood oxygenation at the time of infection, requiring urgent oxygen therapy. CT scans of lung changes revealed that nearly 80% of patients had inflammatory changes in the lungs at the time of diagnosis, with nearly 30% of them affecting over 25% of lung tissue. Importantly, a significant portion of these changes had an advanced nature, indicating both the speed and severity of the inflammatory process [30]. This insidious yet severe course of the disease reflected in a very high mortality rate due to COVID-19 among dialysis patients, close to 31% of those infected, and among patients over 75 years of age, close to 44%, which was nearly 5.5 times higher than in the general population, even after considering the age of patients, which is known to be very high among dialysis patients [23]. In another large, retrospective study from Poland, covering nearly 30% of all dialysis centers, the mortality rate among dialysis patients due to COVID-19 in the years 2020 and 2021 was 12.8% and 21.2%, and these deaths accounted for 13.4% and 16.2% of all deaths among dialysis patients included in the study [31]. It is noteworthy that high COVID-19 mortality rates persisted in 2021 despite a high percentage of vaccination in the studied population, reaching 96% [31]. Similar observations were made in other countries. An observational study conducted in 4 dialysis centers in the Brescia region of Italy showed a 29% mortality rate in the early stages of the pandemic [32]. Multicenter studies from Brazil, New York, Ontario, Scotland, the UK, France, and the Flanders region of Belgium reported mortality rates ranging from 21% to 29.6% [33–38]. The results of the ERACODA study, designed to prospectively collect individual patient data on dialysis patients with COVID-19 across Europe, showed a 28-day mortality rate associated with COVID-19 of 25% for all patients and 33.5% for those requiring hospitalization [39]. As shown in data published in annual reports on the state of renal replacement

therapy in Poland, in the years 2020, 2021, and 2022, 6%, 4%, and 2% of all HD patients in Poland died from COVID-19 within 6 weeks of infection [3, 24, 25].The determinants of such high mortality were thoroughly analyzed in numerous studies. Understanding these factors allowed for the selection of the most vulnerable patients and the implementation of rapid therapy. Risk factors for mortality in the general population included advanced age, male gender, and the presence of comorbidities [40–42]. An analysis of data from a study conducted by our team among HD patients in the Pomeranian Voivodeship showed that the strongest predictor of 3-month mortality was a high frailty score (CFS > 3) and advanced age (> 65 years) [43]. The results are consistent with extensive analyses in the ERACODA report, containing data collected from 98 dialysis centers in Europe [39].

In addition to factors that may worsen patient outcomes, factors which have a positive impact on the course of disease were also postulated. Among these, the presence of blood type O and chronic vitamin D supplementation in the period before SARS-CoV-2 infection were mentioned [30, 44, 45]. One explanation for these associations may be that a blood type other than O is a significant genetic risk factor for venous thromboembolic disease, a well-known prognostic factor in the course of COVID-19 [44, 46]. Low levels of 25-hydroxyvitamin D (25-OH D) are correlated with high levels of IL-6, an independent predictive factor for the severity and mortality of COVID-19 in the general population [47]. On the other hand, the evidence for the effectiveness of vitamin D supplementation in the prevention and treatment of COVID-19 has not been definitively confirmed [48, 49].

POST-COVID SYNDROME

Despite the severe course of the disease, the immune system of most dialysis patients overcomes the SARS-CoV-2 infection. However, recovery, depending on the severity of the symptoms, can take several weeks, and not all symptoms always disappear immediately. A significant proportion of recovered individuals report persistent symptoms, such as cough, shortness of breath, and muscle aches, lasting for several months after the virus has been eradicated [50]. The term "long-COVID" or "post-COVID syndrome" was introduced for this clinical situation. It is defined as the persistence or development of new symptoms 3 months after the initial SARS-CoV-2 infection, and these symptoms should last for at least 2 months [51].

In a prospective cohort study, our team analyzed the long-term health consequences of COVID-19 among HD patients who contracted COVID-19 during the second and third waves of the pandemic in Poland [52]. Only 6.3% and 19% of patients were symptom-free 3 and 6 months, respectively, after hospital discharge, while as many as 72.1% and 53.4% of patients experienced at least 3 persistent symptoms of COVID-19. The most common lingering symptoms included fatigue or muscle weakness (60.76% and 47.04%) and palpitations (40.51% and 30.14%). Before the illness, 21.5% of patients reported shortness of breath at level 1 on the mMRC scale. This percentage increased to 43.03% and 34.25% at 3 and 6 months of observation, respectively. Importantly, persistent symptoms of the disease significantly affected the quality of life of survivors. Patients reported a reduced quality of life, which was noted in all domains of the EQ-5D-5L questionnaire, but especially in the domains of pain, discomfort, and anxiety [52]. There are not many long-term studies on this issue in the population of dialysis patients. However, the results which our team observed correspond relatively well with the findings of a study by Huang et al. [53] conducted in the general population and using diagnostic methods similar to those in our study. In this study, which had a follow-up period of up to 12 months, it was found that at least one persistent symptom was still reported by 49% of patients. Fatigue and muscle weakness were the most commonly reported symptoms [52]. It is worth noting that the actual frequency of post-COVID syndrome varies significantly between different studies and is challenging to objectively estimate. This is due, among other things, to the different populations included in the studies, different definitions of the syndrome, and various diagnostic procedures, mostly based on the subjective assessment of the patient.

In the multicenter national study form Turkey, maintenance HD patients who have had COVID-19 in the past 90 days have increased rehospitalization, respiratory problems, vascular access problems, and high mortality compared with the non–COVID-19 HD patients [54]. In another retrospective study from France, the authors report a high inci-

dence of cachexia in survivors, reaching 13% of those who underwent COVID-19 in the past with a median of 180 days [55].

VACCINATIONS AGAINST COVID-19

The development of vaccines against COVID-19 marked a significant breakthrough in the history of the pandemic, leading to substantial improvements in terms of disease susceptibility, disease course, and long-term prognosis. The first vaccines to undergo all stages of clinical trials were based on mRNA technology, including BNT162b2 (Pfizer--BioNTech) and mRNA-1273 (Moderna). Phase III clinical trials demonstrated their effectiveness in the general population, with efficacy rates of approximately 95% and 94.1%, respectively [56, 57]. These vaccines became available at the turn of 2020 and 2021. Dialysis patients, individuals treated with immunosuppressive drugs, and those with cancer were among the first groups to be designated for population-wide vaccination under the national COVID-19 vaccination program. Despite initial skepticism and concerns about potential side effects, it was possible to achieve a very high vaccination rate in the Polish population of dialysis patients, reaching up to 96% [31]. It turned out that the vaccines were well--tolerated, and the rate of adverse events, in the majority of cases, did not deviate significantly from those observed in large clinical trials conducted in the general population. In a prospective controlled study involving 190 HD patients Polewska et al. [58] analyzed the safety and tolerance of two-dose vaccination regimen using BNT162b2 and demonstrated that 59.8% of patients (dose 1) and 61.4% (dose 2) reported at least one local reaction, while 15.9% (dose 1) and 29.4% (dose 2) reported at least one systemic reaction. Pain at the injection site was the most common local adverse reaction, while fatigue and muscle pain were the most common systemic symptoms. Most local and systemic reactions were observed less frequently than in the control group, matched for age and gender [58].Given the impaired immune response to vaccination observed in patients with CKD, especially during hepatitis B vaccinations, it was suspected that a similar situation might occur following COVID-19 vaccinations [4–6, 59]. Dialysis patients were not included in the clinical registration trials of COVID-19 vaccines. Therefore, their effectiveness in them remained uncertain, and the vaccination schedule for dialysis patients was the same as that for the general population. Data on vaccine effectiveness for dialysis patients come from observational studies conducted during the implementation of population-wide vaccinations. The post-vaccination response in terms of anti-spike protein antibodies was shown to be high in this group. In a cross-sectional study conducted at dialysis center in Gdansk with 126 patients, a post-vaccination immune response appeared in 95.6% of patients [60]. Similar results were observed in other studies [61]. However, the antibody titers measured 14–21 days after the second mRNA vaccine dose were significantly lower than those observed in the general population [60]. A number of studies have analyzed factors that may independently influence poorer post-vaccination immune response. These include in particular: older age, low levels of albumin, IgG, low amount of lymphocytes in the blood, use of immunosuppressants, longer dialysis vintage and use of high doses of intravenous iron [26]. Older age may have a particularly detrimental effect for immune response following vaccination. In the study of Grupper et al. [61] there was shown a significant inverse correlation of older age and IgG anti-s antibodies levels in dialysis patients (Spearman correlation = − 0.29; P = 0.03). Moreover, for each age range, there were higher levels of antibodies in the control group compared with the dialysis group, which was significant for ages < 60 and 60–70 years old [61]. The development of immunologic memory is decreased with age because aged T cells favor the production of short-lived inflammatory effector over memory or follicular helper T cells [62]. Breakthrough infections with the SARS-CoV-2 virus were also common among vaccinated dialysis patients [63]. For these reasons, a common practice in many countries, including Poland, was to provide a third complimentary dose of mRNA vaccine in them after the initial two-dose vaccination regimen.

PROGNOSTIC BREAKTHROUGH

Vaccination against COVID-19 has resulted in a significant improvement in the prognosis of HD patients. In clinical practice, there was a noticeable decrease in infections, a milder course of COVID-19, and reduced mortality. This has been confirmed in numerous observational studies from various centers. In patients who completed the full vac-

cination cycle, the risk of infection was up to 78% lower compared to unvaccinated patients [64, 65]. For those patients who still developed the disease, it often had an asymptomatic character, with fever and lung involvement being rarer, and patients were less frequently hospitalized [66]. Most importantly, it has been confirmed that vaccines reduce mortality from COVID-19. A large multicenter study by Torres et al. [67], which included 12,301 vaccinated HD patients with BNT162b2 and CoronaVac (Sinovac Biotech), demonstrated the effectiveness of these vaccines in preventing death, with a 66% reduction in mortality. The BNT162b2 vaccine, in particular, reduced the risk of COVID-19-related death by 90.4%. Ashby et al. [65], using logistic regression modeling, which accounted for demographic data, comorbidities, and the pandemic period, showed an 88% reduction in deaths in the vaccinated group compared to the unvaccinated group. Results from Poland confirm these trends. In a retrospective study covering all HD patients in the northern region of Poland, our team compared mortality rates during the second and fourth waves of the pandemic, taking into account that most patients were unvaccinated during the second wave, while vaccination rates reached 92% during the fourth wave. The COVID-19 mortality rate during the second wave was 29.5%, but during the fourth wave, among vaccinated patients, it decreased to 6.7%. There was also a 79% reduction in the risk of infection [68]. Promising reports have also emerged from studies conducted in the general population, suggesting the protective effects of vaccinations against the development of long-COVID syndrome [69]. Unfortunately, there is a lack of data on this aspect in relation to HD patients.

The question of how much the development of natural immunity due to SARS-COV-2 infection that occurred before or after vaccination contributed to the improved prognosis remains open. It is important to note that the percentage of confirmed cases before the initiation of vaccinations reached 22.4% in HD patients [23], and some infections may have gone undetected. As it is known, the rate of asymptomatic infections among HD patients reached up to 51% [70]. Some researchers have indicated that infection with the SARS-CoV-2 virus was associated with a lower risk of reinfection with SARS-CoV-2 in general population compared to what occurred after vaccination with two doses of mRNA vaccines (BNP162b2 and mRNA1273). Infection was also linked to a lower risk of severe COVID-19 [71]. However, the highest level of protection against severe COVID-19 disease is undoubtedly provided by hybrid immunity, obtained through vaccination and SARS-CoV-2 infection itself at any order. Hybrid immunity is not only robust but also more durable than either natural immunity alone or vaccine immunity alone [72]. It should also be remembered that the natural course of the pandemic and subsequent mutations of the SARS-CoV-2 led to its weakening, a milder course of the disease and the gradual extinction of the pandemic [73]. Nonetheless, regardless of these considerations, vaccinations remain the only option that effectively protects against primary infection, which can lead to hospitalization, death, and long-term complications.

LESSONS FOR THE FUTURE

The COVID-19 pandemic, which, as it appears, is now behind us, has resulted in thousands of casualties, particularly within the population of patients undergoing HD. However, it can be regarded also as an experimental field to learn how to deal with other rapidly spreading pathogens and future pandemics. It is well-known that a significant factor inherently associated with the risk of various infections in HD patients is their lifestyle. This lifestyle involves visits to dialysis centers several times a week for a few hours. During this time, patients must travel from their place of residence, often using public transportation to reach the dialysis center, where they come into contact with both the staff and other patients who could be a source of infection [74].

One key lesson for the future is the rapid implementation of preventive measures to minimize the spread of the pathogen among patients. The starting point is, of course, the application of basic preventive rules, such as wearing masks (even during the entire dialysis session), hand hygiene, and maintaining physical distance. As we have learned from experience, these methods proved insufficient for HD patients. In the early days of the pandemic, there were no specific guidelines for managing repeated dialysis treatments during a pandemic. Over time, scientific societies and public health authorities issued universal preventive measures to be used in dialysis units, with locally developed precautions added to daily

practice [75, 76]. One of the first steps taken was designating dedicated dialysis centers for patients with confirmed SARS-CoV-2 infection. Later in the pandemic, after most patients had been vaccinated, patients with confirmed infection were segregated locally in dialysis units, either in separate dialysis rooms or on different shifts. Separate communication pathways within the dialysis units were established. To reduce the time patients spent in dialysis units, the duration of dialysis sessions and weekly dialysis frequencies were reduced to the necessary minimum that was safe for each patient, overlooking the adequacy of dialysis in this exceptional epidemiological situation. Patients were prohibited from consuming meals in dialysis units, and communal meals among the staff were also prohibited. Individual patient transport to and from the dialysis units was organized, or patients were advised to use their own transport when an infection was confirmed or suspected [77]. This allowed a reduction in the contact between healthy patients and those infected or suspected of infection. Enhanced hygiene rules also applied to the staff to minimize transmission of the virus within the patient-staff-patient chain. Some dialysis units imposed strict personnel division, where specific individuals were permanently assigned to work on specific shifts. Some dialysis units conducted periodic screening tests for asymptomatic SARS-CoV-2 infection among patients and staff [74, 76, 78]. In the study conducted in the dialysis units of the Pomeranian Voivodeship by Biedunkiewicz et al. [76], lower incidence rates of COVID-19 were found in units that avoided concurrent dialysis for patients coming from home and hospitalized patients.

Procedures were also introduced to quickly identify infected individuals. To achieve this, telephone interviews with patients regarding their well-being and potential exposure to infection were conducted. Patients were required to report any concerning symptoms and contact with infected individuals. Temperature measurements were taken before entry into the dialysis unit. In this discussion, the issue of home HD is intentionally overlooked, as it would undoubtedly provide the highest level of protection for the patient against infection. However, it is not yet available to Polish patients. If home HD methods become widespread, they should be the preferred methods in times of pandemic. It is worth mentioning here that peritoneal dialysis (PD), which is beyond the scope of our study, has proven to be a much safer alternative in treating patients with end-stage renal failure during the COVID-19 pandemic. According to information from the report on dialysis therapy in Poland in 2020, only 6% of the PD patient population contracted COVID-19, compared to staggering 21% among HD patients [24]. There is no doubt that patients on PD were able to significantly limit interpersonal contacts. Therefore, some authors conclude that PD should be the renal replacement therapy of choice in the periods of a pandemic, regardless of the pathogen causing it [79].

Another important lesson learned from the COVID-19 pandemic was the prioritization of HD patients and the prompt initiation of vaccinations. European countries implemented these principles right away, and the United States followed suit after some time. Such actions undoubtedly saved many lives within this patient population. Considering the high vulnerability of HD patients to severe infectious diseases, this principle should also apply in the case of future grave pandemics. The COVID-19 vaccinations have confirmed that the basic vaccination regimen tailored to the general population may be insufficient to induce an adequate immune response in HD patients [60]. Hence, it is justifiable to monitor the immune response in this group of patients and contemplate the use of supplementary vaccinations, as was the case with COVID-19 vaccinations.

Conflict of interest

The authors declare no conflict of interest.

Founding:

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