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REVIEW

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Reasons and consequences of COVID-19 vaccine failure in patients with chronic lymphocytic leukemia

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Abstract

People with hematologic malignancies are at a high risk of morbidity and mortality from COVID-19. The response to vaccination is highly limited in patients with chronic lymphocytic leukemia. Less than half of the patients develop antibody response, suggesting that they remain at risk of SARS-CoV-2 infection even after the vaccination. Reasons for inadequate response to COVID-19 vaccination in chronic lymphocytic leukemia are multifactorial and attributed to disease-related immune dysregulation and patient- and therapy-related factors. The negative predictors of response to vaccination include hypogammaglobulinemia, advanced age, current active treatment, and past treatment anti-CD20 monoclonal antibodies. Despite using booster doses and heterologous immunization to improve humoral and cellular immunity, some patients with chronic lymphocytic leukemia will fail to respond. Active treatment at the time of vaccination and a recent history of anti-CD20 monoclonal antibodies use are the strongest predictors of the non-response. Current data support informing patients with chronic lymphocytic leukemia and other hematologic malignancies about the risk of infection regardless of vaccination. These individuals and members of their households should continue extreme preventive actions despite relaxed local regulations. Other emerging non-vaccine preventive strategies include passive and post-exposure prevention with monoclonal antibodies.

KEYWORDS
chronic lymphocytic leukemia, COVID-19, hematologic malignancies, passive prevention, post-exposure prevention, vaccine

Novelty statement: What is the new aspect of your work?

• After approval of COVID-19 vaccines and broad vaccination campaigns in many countries, it appeared that patients with cancer and especially with hematologic disorders develop only limited protection from the infection. Based on the accumulated data, patients with chronic lymphocytic leukemia (CLL) are at the highest risk of COVID-19 infection regardless of vaccination. However, it is not possible to identify a single reason for observed lower antibody titers.

What is the central finding of your work?

• Multiple factors contribute to inadequate response to COVID-19 vaccination in CLL. Patients with the early-stage disease without active treatment have the highest likelihood of an adequate response to vaccination. The review presents multifactorial reasons attributed to disease-related immune dysregulation patient and therapy-related factors and discusses their importance. However, it does not cover the medical need of all patients with CLL.

What is (or could be) the specific clinical relevance of your work?

• These patients are a priority group for vaccination and following extended activities to leverage the vaccines efficacy, passive and post-exposure protection. Current guidelines and policies are presented. Recently, the third booster dose of mRNA vaccine was approved in the US for vulnerable populations. Some European countries already started to apply this strategy locally; however, it is already known that some patients with CLL fail to respond. The use of non-vaccine protection in these patients is a priority.

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1 | IMPACT OF COVID-19 PANDEMIC ON PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

Since the beginning of the coronavirus disease-2019 (COVID-19) pandemic, cancer patients have been regarded as a vulnerable population. Elderly, frail, and affected by significant comorbidities cancer patients were especially susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection and are more likely to develop severe disease, with a high risk of death than in the general population.[1-4] The mortality estimated in the meta-analysis in adult onco-hematological patients with COVID-19 was 34%. Every three out of four patients required hospitalization.[5] Multicenter studies showed that patients with chronic lymphocytic leukemia (CLL) had a high risk of morbidity and mortality from COVID-19.[6,7] This strongly supported the recommendation to prioritize COVID-19 vaccination for patients with hematologic cancer.[8] National and international healthcare institutions adapted guidelines regarding priority vaccination against COVID-19 in this vulnerable patient population.[9-14]

2 | RESPONSE TO COVID-19 VACCINES IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

In the absence of efficacious treatment of COVID-19, registration of first vaccines was the greatest promise to end the pandemic. Whether COVID-19 vaccination will be protective in the population of patients with hematologic malignancies, particularly in patients in advanced age and profoundly immunosuppressed due to disease and cytotoxic cancer treatments, was the primary concern of hematologists during the development of vaccines. Patients with CLL are burdened with these factors and already in past showed compromised responses to different immunizations.

More specifically, serological response to pneumococcal, haemophilus, hepatitis B, zoster or influenza vaccines was adequate typically in patients at the early stage of the disease, before chemotherapy and the development of hypogammaglobulinemia.[15-21] It indicates it would be more advantageous to vaccinate early after CLL diagnosis. Attempts to optimize seroconversion by alternative vaccination schemes like booster doses and sequencing different vaccines had mixed results.[20,22,23] Comparison of efficacy of pneumococcal conjugate and polysaccharide vaccines revealed differences in immune response[24]; it highlights the role of type of vaccine; however, adequate response to the more beneficial conjugate vaccine was still lower than in healthy controls.[25] Immune enhancement of the response to vaccination with lenalidomide or granulocyte-macrophage-colony-stimulating factor was not significant[23,26]; however, ranitidine stimulated antibody response to the polysaccharide vaccines.[27] The finding requires further studies.

Pivotal clinical trials evaluating efficacy and safety of the SARS-CoV-2 vaccines[28-31] did not provide information about the effectiveness of vaccinations in patients in immunosuppressive or immunodeficient states or receiving systemic immunosuppressants or immune-modifying drugs since they were excluded from studies. Approved in Europe vaccines against SARS-CoV-2 are mRNA or vector-based and can be used in patients with CLL without risk of dissemination of attenuated virus from a vaccine.[32,33] In addition, a large study confirmed safety of BNT162b2 mRNA COVID-19 vaccine in patients with CLL.[34]

Concerns about efficacy of COVID-19 vaccines in patients with CLL occurred justified. Immune response to vaccination was severely impaired in patients with CLL. The proportion of patients with antibody response to COVID-19 vaccines varied from 23% to 47% (Table 1)[34-38] and was lower compared to patients with other hematologic malignancies and healthy controls.[37-40] Agha et al.[37] showed that patients with CLL were significantly less likely to develop SARS-CoV-2 antibodies than patients with other hematologic malignancies (23.1% vs. 61.1%, $p = .01$). This, in combination with advanced age and other comorbid conditions, put patients with CLL at increased risk of morbidity and mortality from SARS-CoV-2 infection, despite the protective role of vaccines in the broad population.

It should be noted that the SARS-CoV-2 vaccine induces both humoral and cell-mediated immunity; however, most of the studies involving patients with hematologic malignancies focus on the production of neutralizing antibodies against the spike protein only. The serologic response is considered a surrogate endpoint of immunity. The response to the vaccination itself is more complex than only the titer of antibody, e.g., the seropositivity after vaccination may not equal virus neutralization capability in patients with B cell malignancies.[41] In addition, the vaccine's T cell immune efficacy can be higher than serological efficacy in patients with hematologic malignancies.[42]

TABLE 1 Seroconversion after the two doses of mRNA vaccine in patients with chronic lymphocytic leukemia

Study	*N*	% of patients with antibody-mediated response to the vaccine[a]
Benjamini et al. (2021)[34]	473	43%
Herishanu et al. (2021)[35]	167	39.5%
Agha et al. (2021)[37]	13	23.1%
Roeker et al. (2021)[64]	44	23%
Tzarfati et al. (2021)[38]	34	47%

[a]CONCENTRATION of antibodies judged as the seropositivity may vary between studies.

In CLL, cellular immune responses, similar to the humoral response, are suboptimal due to T cells' structural and functional defects.[43] The SARS-CoV-2 infection itself was accompanied by decreased levels and exhaustion of T cells.[44] Decreased levels of CD5+ and CD8+ T cells could be a possible risk factor of a severe course of the COVID-19 in the group of fit patients treated with venetoclax-based combinations as part of the GAIA/CLL12 trial.[45] Thus, pre-existing and treatment-associated cellular defects might lead to an impaired T cell response in patients infected with COVID-19 and vaccinated. Up to now, only a few reports have provided information about cellular response to the COVID-19 vaccination in CLL. In patients with CLL, both the mRNA and vector-based COVID-19 vaccines may generate the spike protein-specific T cells able to release interferon.[46-48] The cellular response can be present in the absence of the humoral. However, the current knowledge is limited to case reports and small series of patients, and it needs to be evaluated in large studies.

3 | PATIENTS WITH CLL, AS THE POPULATION AT A HIGH RISK OF NON-RESPONSE TO COVID-19 VACCINE

CLL affects <1 to 5.5/100,000 of the population at any time. Patients with CLL represent from 22 to 30% of all patients with leukemia.[49] Because of lack of functional B cells and impaired humoral immunity, they are prone to infections, a cardinal feature of CLL.[50] Also, poor humoral response to different vaccinations was well-documented within this population.[16,17,21,24] Reasons for poor response to COVID-19 vaccination are multifactorial and attributed to disease-related immune dysregulation and patient- and therapy-related factors (Table 2).

3.1 | Disease-related factors

Infections are the major disease-specific feature of CLL, and the tumor burden is a leading factor influencing immune function. Tumor cells slowly replace immune cells in lymphoid tissues; however, impairment of immune function occurs even during an early-stage disease, at relatively small tumor infiltration.[51] Although the severity of immune suppression in CLL increases with time from diagnosis, the risk of infection had a constant pattern in over ten years of observation of 125 patients with CLL.[52] Tumor cells suppress natural immune function by release of interleukins, cytokines, chemokines,[53] and presenting surface proteins[54] which modify the function of normal B and T cells leading to characteristic changes of their phenotype and impaired signaling between B and T cells.[43,51,55-57] The clinical and molecular heterogeneity of CLL patients is well-known.[58] Since the production of antibodies against the S protein depends on proper T and B cell interaction, both quantitative and qualitative humoral and cellular defects in immune cells reduce response to vaccines.

Hypogammaglobulinemia correlates with infection risk[59] and has been an independent factor associated with poor humoral response to COVID-19 vaccines.[34,35] Concentrations of IgG <550 mg/dl and IgM <60 mg/dl were negative predictors of response to BNT162b2 mRNA COVID-19 vaccine in patients with CLL[35] (Table 2). The normal concentration of IgA was a predictor of good response after the second vaccine in multivariate analysis.[60] Fox T. et al.[41] showed that CD19, CD4, and CD56 counts were significantly associated with seropositivity after the vaccination in the cohort of patients with B cell malignancies, including CLL. Low antigens count and total blood lymphocytes were associated with low anti-spike protein antibody positivity. It aligns with studies involving only CLL patients, where immunoglobulin levels correlated with a higher seropositivity rate (Table 2). This suggests that a higher humoral response to vaccination can be expected when lymphocyte populations and globulin levels recover. The finding has important implications for the proper timing of the vaccination in the course of the disease.

3.2 | Patient-related factors

The median age at the time of the CLL diagnosis is 64 years.[61] Both COVID-19 fatalities[62] and impaired vaccine responses[63] are more common in older adults. In all studies evaluating response to COVID-19 vaccines, the older age was an unfavorable prognostic factor[34,35,37,38,64] (Table 2). However, the observed lack of even minimal antibody response to the COVID-19 vaccine cannot be explained purely by age. As mentioned before, immune dysfunction develops with the duration of the disease, thus is associated with disease-specific humoral defects.

Typically, females develop higher antibody responses following vaccination than males.[65] This was also true in patients with CLL[35] (Table 2).

3.3 | Treatment-related factors

The treatment options, such as anti-CD20 antibodies and Bruton Tyrosine Kinase inhibitors (BTKi), can significantly affect response to different vaccines[21,66-69] (Table 2). Patients with CLL under active surveillance or without active treatment produced antibodies followed the COVID-19 vaccine more than people on treatment.[34,35,38,40,41,60,64] The number of prior treatment lines did not influence the seropositivity rate. The antibody response rate in patients receiving BTKi was 16.0% and 13.6% in patients treated with venetoclax with anti-CD20 antibodies. Ongoing or recent treatment with BTKi or CD20 antibody significantly decreases humoral response to vaccination; however, 62% of patients treated with an inhibitor of BCL-2 (venetoclax monotherapy) developed immune response.[34] A low rate of seropositivity was observed in the group of patients treated with JAK2 inhibitors, too. Patients who underwent HSCT had a similar rate of seropositivity as those who did not.[38]

TABLE 2 Independent negative predictors of antibody response to mRNA-based COVID-19 vaccine in patients with chronic lymphocytic leukemia

		Serologic response (%)		Multivariate analysis	
	N [reference]	Positive	Negative	OR (95% CI)	*p*-value
Disease-specific factors					
IgG <700 mg/dl	130[34]	28%	72%	0.736 (0.420–1.291)	.0012[m]
IgG <550 mg/dl	46[35]	15%	85%	0.27 (0.79–0.92)	.037[m]
IgM <40 mg/dl	166[34]	26%	74%	0.394 (0.238–0.649)	<.001[m]
	87[35]	23%	77%	0.34 (0.14–0.82)	.017[m]
Patient-specific factors					
Age >70 years old	165[34]	37%	63%	0.65 (0.43–0.98)	.04[m]
Age ≥70 years old	NR[64]	NR	NR	0.083 (0.020–0.345)	.001[u]
Age >65 years old	117[35]	34%	66%	0.31 (0.11–0.86)	.025[m]
Male sex	222[34]	43%	57%	0.99 (0.65–1.5)	.96[m]
	112[35]	32%	68%	0.27 (0.11–0.68)	.006[m]
Treatment-specific factors					
Any current active treatment	75[35]	16%	84%	0.15 (0.05–0.43)	<.001[m]
	18[64]	NR	NR	0.060 (0.013–0.277)	<.001[u]
Current BTKi treatment	79[34]	6%	82%	0.058 (0.007–0.319)	.0029[m]
	50[35]	16%	84%	NR	NR
	14[64]	NR	NR	0.14 (0.31–0.60)	.009[u]
Any past treatment	26[64]	NR	NR	0.017 (0.002–0.161)	<.001[u]
Time since anti-CD20 treatment <12 mo	39[34]	5%	95%	0.087 (0.005–0.510)	.0256[m]
	22[35]	0%	100%	0.026 (0.001–0.454)	<.001[u]
	14[64]	NR	NR	0.071 (0.013–0.39)	.002[u]

Note: Data from three studies involving only patients with chronic lymphocytic leukemia were reviewed to list the number of patients exposed to a risk factor, the proportion of vaccine responders, and non-responders, and the result of multivariate or univariate analysis (Odds ratio (OR) with 95% confidence interval (CI) and *p*-value). If a factor was not included in the multivariate analysis ([m]) or analysis was not performed, the result of the univariate analysis was presented ([u]). If a study presented factors associated with favorable serologic response, the result was recalculated to present an odds ratio with 95% confidence interval for the negative outcome.

Abbreviation: NR, not reported.

Time from the end of systemic therapy to vaccination plays a role in response to the vaccine since the effect of drugs maintains after the completed treatment.[38,41] It was not likely that patients treated with anti-CD20 antibodies within the last 12 months would respond to COVID-19 vaccination[35,38,64] (Table 2). It is consistent with earlier meta-analysis findings; response to different vaccinates improves incrementally after anti-CD20 therapy.[68] Fox T. et al.[38] found that patients who completed any anti-CLL treatment more than six months before vaccination were more likely to develop antibodies in comparison with the period shorter than six months between treatment and vaccination.

Since the drugs used to treat CLL are frequently used in other indications, the above may have implications for COVID-19 vaccinations and other states and diseases. Results of populational studies confirmed that patients treated with BTKi, venetoclax, ruxolitinib, or anti-CD20 antibody therapies showed poor antibody responses to the vaccine.[70] BTKi were considered as a possible treatment for COVID-19, but clinical trials evaluating the role of BTKi in the treatment of patients with COVID-19 did not meet the primary endpoints of survival and respiratory failure freedom.[71,72]

4 | CURRENT STANDARDS OF PREVENTION OF COVID-19 IN PATIENTS WITH CLL

Despite the lower seroconversion rate in patients with CLL and other hematologic malignancies, vaccines remain the cornerstone for SARS-CoV-2 infection prevention. In general, patients with cancer should be prioritized for vaccination. Studies in different populations of patients with hematologic malignancies, including transplant patients, confirmed the safety of vaccines. Contraindications and reasons to delay the vaccination of patients with hematologic malignancies are the same as for the general population. Immunization against SARS-CoV-2 is recommended regardless of the presence of factors known to limit humoral response to vaccines (Table 2);

however, emerging efficacy data gave an insight about the best timing of vaccination. Patients with the early-stage CLL without active treatment have the highest likelihood of an adequate response to vaccination. Thus, to avoid suboptimal vaccine efficacy, physicians should recommend vaccination right after the diagnosis or preceding active treatment if possible.

Treatment with BTKi, JAK2 inhibitor or anti-CD20 antibody would impact response to different vaccines, including the COVID-19 vaccines. Despite the current recommendation to vaccinate even if the patient receives active treatment,[9] the likelihood of success in CLL is very low. The recommendation considers the good safety profile of SARS-CoV-2 vaccines, which justifies it even if the expected degree of protection is lower than observed in the general population.[11] Nevertheless, patients with CLL receiving active treatment or recently treated with anti-CD20 antibody most likely will not get protection from the vaccine. The odds for response are extremely low (Table 2).

Patients treated with HSCT or CAR T cell therapy should be vaccinated at least three months post-transplantation/cellular treatment.[9,12] Depending on a local incidence of the infection, this can be extended to 6 months[11] in line with the data about immune system recovery after the treatment.[73] Vaccination >6 months after HSCT was supported with data from the Lithuanian cohort ($n = 885$), showing that serological responses were low within the first 6 months after HSCT but improved afterward.[70] Patients scheduled to undergo cytotoxic or B lymphocytes-depleting therapies should be vaccinated prior to therapy and allowed at least two weeks to pass after the second dose to allow memory T cell formation.[12]

The vaccination schedule should always include two doses of vaccine since the response to a single dose in patients with cancer is minimal, and the second dose of the vaccine is essential in increasing vaccine effectiveness.[42,60] Parry et al.[60] showed that extended dosing schedule of mRNA and adenovirus-based vaccines, with 10–12 weeks delay of the second dose, had encouraging results with 75% of patients seropositive. This was higher than the response rates achieved in studies using standard two-dose regimens of mRNA vaccine (Table 1). However, a long interval between doses is justified at the time of pandemic.

There were controversies about the rationale of using the third booster dose of vaccines in the general population.[65] Nowadays, many countries recommend using a third dose in vulnerable populations, including immunosuppressed patients and healthcare practitioners.[74,75] The evidence about the effectiveness of booster dose in patients in CLL is nowadays limited only to 17 cases.[47,48] Patients without antibodies before the third dose remained antibody-negative; patients with antibodies increased their titers after the third dose. Moreover, the booster dose can induce T cell response and interferon secretion; however, the effect largely depends on treatment during the vaccination sequence. These preliminary data support early use of the third dose; however, some patients will still face vaccine failure.[47] Results of the second study, with only two patients, are promising to patients who did not seroconvert after the mRNA-base vaccine. The use of Ad26.COV2.S vaccine let to antibody response in one patient and boost of T cell response in both patients.[48]

The proper timing of vaccination of patients with CLL after recovery from COVID-19 is unknown. Similar to the vaccination, antibody response after recovery from COVID-19 is also diminished in patients with CLL. Only two of three patients had detectable anti-SARS-CoV-2 IgG within 2 months after the infection, and hypogammaglobulinemia was negatively associated with the seroconversion.[36] The decline in the level of protective antibodies after SARS-CoV-2 infection can be faster than in the general population[36]; thus, nowadays, clinicians need to judge the postponement of vaccination individually based on the risk assessment,[12,76] rather than following the three-month postponement recommended for the general public.

Up to date, none of the studies showed differences in the safety and efficacy of mRNA or adenovirus-based vaccine in patients with hematological malignancies. In patients with CLL, mRNA vaccines (BNT162b2 and mRNA-1273) were the most studied, followed by a two-dose regimen of adenovirus-based vaccine (ChAdOx1), and there were no studies with a single-dose vaccine (Ad26.COV2.S).

Since patients with CLL may be at a high risk of COVID-19 infections,[6] including the time after complete vaccination,[35,38,41,60,64] they need to be adequately informed about the potential lack of efficacy. The vaccination status itself does not preclude immunity in the group of patients with CLL. Consequently, they need to take additional measures to mitigate the risk of disease, e.g., use masks, sanitize or wash hands, and keep social distance. Any changes in policies that relax preventive measures in the general population that follow the virus transmission rate should not apply to immunodeficient patients until herd immunity is gained or the end of the pandemic. In addition, all close contacts of patients should be vaccinated to prevent the spread of the virus in a household. Caregivers, similar to patients, should be recognized as priority groups for vaccination.[9]

Since the measurement of SARS-CoV-2 antibody responses is not the standard outside studies, some authors recommended setting it as a routine screening measure in immunocompromised patients.[37] This would help patients to self-guide the ongoing preventive behavior. Ammad Ud Din M. and Jamshed S. recommended checking anti-S protein IgG titers four weeks after completing vaccination cycle in the high-risk patients.[76] Nowadays, appropriate tests are widely commercially available in Europe.

5 | NEED OF NOVEL STRATEGIES TO PREVENT COVID-19

The current knowledge about the effectiveness of COVID-19 vaccines in patients with hematologic malignancies and recipients of HSCT develops in parallel with the global vaccination campaign. Evidence about safety and efficacy of new vaccines accumulates rapidly and drives changes in clinical practice. Single clinical centers and collaborations provide an increasing amount of data about vaccination outcomes of patients with hematologic malignancies

and underline that such patients are less likely to have a humoral immune response to COVID-19 vaccination. We should expect near-future new emerging data that may influence the primary prevention strategies in this highly vulnerable population since the medical need remains unmet.

There are many unanswered questions, with the main one being about the extent of the risk reduction for SARS-CoV-2 infection after vaccination. As the duration of immunity provided by vaccines in the general public is still unknown, it is also difficult to conclude about the vaccine-induced protection in the group of patients with hematologic malignancies. We await more extended follow-up studies, which will show how patients who developed antibody response would maintain it throughout time.[70] Our current knowledge about protection derives mainly from serum antibody titers and does not include data about the memory B cell responses. Aware of the negative impact of active treatment, it would be reasonable to hold on treatment in patients with the stable disease to allow for an antibody response to the vaccine. However, we lack the data and clinical expertise about it.

A few new approaches are developing to achieve an adequate immune response in non-respondents to vaccination. The first approach is in line with the current discussion and decisions about using booster doses of vaccines to increase immunogenicity and protect from the Delta variant of SARS-CoV-2. The third vaccination might elevate antibody responses in patients with CLL to levels seen in healthy individuals after the second dose. The third dose administrated two months after the second in solid organ transplant recipients improved immunogenicity and prevented SARS-CoV-2 infection.[74,77] Fox et al.[41] suggested that such an approach would benefit patients with CLL if they have been vaccinated within six months of active therapy. Already in France, immunocompromised patients are eligible to receive the third dose of vaccine.[78] The third dose is administrated early, from 3 to 4 weeks after the second.[47] Another helpful approach may include heterologous vaccination (use of mRNA and adenovirus-based vaccines in the vaccination cycle); however, it seems to be a safe and effective way of immunization in the general population,[79] and preliminary report in patients with CLL was promising and did not raise safety concerns.[48]

Finally, passive immunization via monoclonal antibodies or high-titer convalescent plasma has been shown to reduce viral load and reduce COVID-19 complications.[80] Neutralizing antibodies and convalescent plasma were of particular interest for therapeutic purposes but also for prophylactics. Passive immunization has established preventive applications.[81] In the USA, the monoclonal antibodies cocktail, casirivimab and imdevimab, was authorized for post-exposure prophylactics for COVID-19. The cocktail of two antibodies against the SARS-CoV-2 spike protein reduced the risk of developing symptomatic COVID-19 by 92.6% compared to placebo in the group persons received the treatment within 96 hours after household contact with an infected person.[82] When the product becomes available, it may be useful for the post-exposure protection of people at high risk for progression to severe COVID-19, hospitalization and death, like patients with CLL.

6 | SUMMARY

The combination of disease-, patient-, and treatment-related factors makes people with CLL extremely vulnerable to SARS-CoV-2 infection and low-responsive vaccination. We are at the period of rapid learning about predictors of an unfavorable response to vaccination and new approaches to overcome the current care limitations. Despite a high level of non-response in patients with hematologic malignancies, vaccines remain a cornerstone of COVID-19 prevention. Until the achievement of herd immunity or the end of the COVID-19 pandemic, patients with CLL need to adhere to strict preventive measures, regardless of their vaccination status.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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